Neifeld Docket No: TACT0019

NEIFELD REF.: TACT0019

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Application No.	: 09/841,844	Confirmation No. 5830
Patent No.	: 6,537,549	Issued: March 25, 2003
Applicant	: Edward L. Tobinick	
Filed	: 05/25/2001	
TC/A.U.	: 1615	
Examiner	: CHANNAVAJJALA, LAKSHMI SARADA	

37 CFR §1.78 Petition for Acceptance of an Unintentionally Delayed Claim for Priority and Petition for Entry of an Amendment to the Specification in an Issued Application

This is a Petition to accept an unintentionally delayed claim of priority under 37 CFR 1.78(a)(3). The entire delay between the date the priority claim was due under paragraph 37 CFR 1.78 (a)(2)(ii) and the date of submission of this Petition was unintentional.

The fee required by 37 CFR 1.17(t) is submitted herewith.

An amendment to the specification correcting the reference to related applications is submitted herewith.

A draft Certificate of Correction for U.S. 6,537,549 and the fee required by 37 CFR 1.20(a) are submitted herewith.

All of the elements required under 37 CFR 1.78(a)(3) have been presented, thus awarding a corrected priority chain in application Ser. No. 09/841,844 is proper.

I. STATEMENT OF THE RELIEF REQUESTED

The applicant petitions for acceptance of an unintentionally delayed claim for priority and for entry into this issued application of an amendment to correct the benefit claim under 35 U.S.C. §120.

The chain of priority in 09/841,844 is missing a reference to application 09/666,068. And as explained below, the priority chain should specify that 09/826,976 is a continuation-in-part of 09/666,068.

The priority chain of 09/666,068 (US 6,379,666) is itself the subject of a petition for acceptance of an unintentionally delayed claim for priority, that was filed on March 30, 2010. The Certificate of Correction filed with that petition was issued by the PTO on April 27, 2010.

Also, the priority chain of 09/826,976 (US 6,419,944) is itself the subject of a petition for acceptance of an unintentionally delayed claim for priority, that was filed on May 28, 2010. The Certificate of Correction filed with that petition has not yet issued..

The present petition relies on the priority chain of 09/666,068 as corrected in the petition filed on March 30, 2010 and the priority chain of 09/826,976 as corrected in the petition filed on May 28, 2010. The material facts recited below pertaining to the file history of 09/666,068 are essentially the same as in the earlier petitions, and all identical exhibits in the related petitions have the same exhibit numbers.

In an Amendment submitted herewith, page 1 of the specification (the paragraph starting with "RELATED APPLICATIONS") is amended as follows (marked-up):

> -- This is a continuation-in-part of application Ser. No. 09/826,976, filed on Apr. 5, 2001, now U.S. Pat. No. 6, 419,944, which is a continuation-in-part of application Ser. No. 09/563,651, filed on May 2, 2000, was now U.S. Pat. No. 6,471,961, and a continuation-in-part of application 09/666,068, filed on December 11, 2000, now U.S. Pat. No. 6,379,666, which is a divisional ~~continuation-in-part~~ of application Ser. No. 09/476,643, filed Dec. 31, 1999, now U.S. Pat No. 6,177,077, which is a continuation-in-part of Serial No. 09/275,070, filed March 23, 1999, now U.S. Pat No. 6,015,557, which is a continuation-in-part of application Ser. No. 09/256,388, filed on Feb. 24, 1999, now abandoned. --

II. MATERIAL FACTS

A. CHAIN OF APPLICATION FILINGS

1 On February 24, 1999, the applicant filed Serial No. 09/256,388, with an original U.S. inventor declaration.

2. On September 16, 1999, applicant filed a notice of express abandonment that stated:

"Re: S.N. 09/256,388 Applicant hereby abandons the above-identified application in favor of Appln. S.N. 09/275,070, which has been allowed by Examiner Jarvis."

3. Serial No. 09/275,070 was filed on March 23, 1999, and matured into U.S. 6,015,557 on January 18, 2000. The applicant filed an original U.S. inventor declaration in 09/275,070, which specifically referred to S.N. 09/256,388.

4. Applicant filed Serial No. 09/476,643 on December 31, 1999, which is prior to January 18, 2000, and was therefore co-pending with S.N. 09/275,070. Applicant filed an original U.S. inventor declaration attached to the specification in 09/476,643 that did not refer to any prior applications.

5. Page 1 of the '643 specification, under the heading "RELATED APPLICATION" stated erroneously that "This is a continuation-in-part of Application Serial No. 09/256,388, filed on February 24, 1999." This statement is erroneous because 09/256,388 had been expressly abandoned on September 16, 1999 (before the '643 application was filed) in favor of 09/275,070 which was still pending when the '643 application was field.

6. On July 21, 2000, applicant filed a "new" (i.e, a second) original U.S. inventor declaration in 09/476,643 that specifically refers to 09/256,388 and to 09/275,070, thus correcting priority and preserving co-pendency throughout all applications in the chain.

7. Serial No. 09/476,643 matured into U.S. 6,177,077 on January 23, 2001. On page 1 of the patent specification, as amended on July 21, 2000, it states "This application is a continuation-in-part of Ser. No. 09/275,070, filed March 23,1999, now U.S. Pat No. 6,015,557, which is a continuation-in-part of application Ser. No. 09/256,388, filed on Feb. 24, 1999, now abandoned."

8. Applicant initially submitted divisional Ser. No. 09/666,068 (which is the application now being added to the priority chain of the subject application) on September 19, 2000, but later it was accorded the official filing date of December 11, 2000, which date is still prior to

January 23, 2001. Thus, divisional 09/666,068 was co-pending with its parent application 09/476,643. The applicant filed the same inventive specification, a copy of the U.S. inventor declaration from 09/476,643, and relied upon that copy of the original inventor declaration to secure the December 11, 2000 filing date.

9. Claims 1 - 23 and 30 - 38 of application 09/826,976 recite methods for inhibiting the action of TNF for treating various medical conditions by administering a TNF antagonist. The specification of application 09/666,068 contains disclosure relating to the claimed methods in 09/826,976, and, therefore, the '068 application should be added to the priority chain of application 09/826,976. (That change in the priority claim was the subject of a Petition filed on May 28, 2010, for US 6,419,944.)

10. On 12/06/2000, applicant filed a request for Correction of Filing Receipt in 09/666,068 stating erroneously: "THIS APPLICATION IS A DIV OF 09/476,643, DATED 12/31/1999, WHICH IS A CIP OF 09/256,388, DATED 2/24/1999, ABANDONED." This statement was erroneous because 09/476,643 is actually a continuation-in-part of Ser. No. 09/275,070, and because it cannot be a continuation-in-part of 09/256,388, due to lack of co-pendency, as explained above.

11. On 11/15/2001, the Related Application statement on page 1 of application 09/666,068 was amended by the Examiner (as indicated by handwritten, dated initials) to add the following underlined text: "This application is a divisional of Ser. No. 09/476,643, filed Dec. 31, 1999, now U.S. Pat No. 6,177,077, which is a continuation-in-part of Application Ser. No. 09/256,388, filed on Feb. 24, 1999, now abandoned." This statement is erroneous because 09/476,643 is actually a continuation-in-part of Ser. No. 09/275,070, and because it cannot be a continuation-in-part of 09/256,388, due to lack of co-pendency, as explained above.

12. On 02/22/2001, an Official Filing Receipt was issued in 09/666,068 stating "THIS APPLICATION IS A DIV OF 09/476,643, 12/31/1999, PAT 6,177,077 WHICH IS A CIP OF 09/256,388, 2/24/1999, ABANDONED." This statement is erroneous because 09/476,643 is in fact a continuation-in-part of Ser. No. 09/275,070, and it cannot be a continuation-in-part. 09/256,388, due to lack of co-pendency, as explained above.

13. So in 09/666,068, the applicant's request for Correction of Filing Receipt (12/06/2000), the Examiner's amendment to the specification (11/15/2001), and the Official Filing Receipt

(03/22/2001) are all incorrect. That is because 09/476,643 is actually a continuation-in-part of Serial No. 09/275,070, while 09/275,070 is a CIP of 09/256,388.

14. As a result of these facts the 09/666,068 application contained an erroneous priority chain, which error was the subject of a Petition filed on March 30, 2010 for acceptance of an unintentionally delayed claim for priority which has yet to be formally granted. However, a Certificate of Correction regarding the priority chain in 09/666,068 was issued on April 27, 2010.

15. Accordingly, application 09/666,068 is properly called a divisional of application Ser. No. 09/476,643, as recited in the Amendment submitted herewith.

16. Applicant filed Ser. No. 09/563,651 on May 2, 2000, which date is prior to January 23, 2001 (when 09/476,643 matured into U.S. 6,177,077), along with an original U.S. inventor declaration signed May 2, 2000 that claims benefit to application 09/476,643. The first page of 09/563,651 did not refer to any related cases. It issued as U.S. 6,471,961 on October 29, 2002. A Certification of Correction was issued May 23, 2006, correcting the priority chain, by claiming benefit to application 09/476,643, related as a CIP.

17. Applicant filed Ser. No. 09/826,976 on April 5, 2001, with an original U.S. inventor declaration signed April 4, 2001. The first paragraph of the '976 specification contains the priority chain essentially as it appears in the issued patent, U.S. 6,419,944.

18. Applicant filed subject application 09/841,844 on April 25, 2001, with an original U.S. inventor declaration signed April 20, 2001. The first paragraph of the '844 specification contains the priority chain essentially as it appears in the issued patent, U.S. 6,537,549.

B. USPTO RECORDS SHOWING THE BENEFIT CLAIM IN 09/841,844

19. Exhibit 26 is copy of the 1 page transmittal letter, and page 1 of the specification filed on 04/25/2001 in application 09/841,844. The upper left hand corner of Exhibit 26 has a USPTO date stamp showing "04/25/01." The upper right hand corner shows the USPTO application "09/841,844."

20. Exhibit 26, page 2 shows the original first sentence of the specification along with the examiner's handwritten amendment dated 01/1/02 revising the priority claim to recite "This is a continuation-in-part of application Ser. No. 09/826,976, filed on April 5, 2001, now U.S. Pat.

No. 6,419,944, which is a continuation-in-part of Application Serial No. 09/563,651, filed on May 2, 2000, now U.S. Pat. No. 6,471,961, which is a continuation-in-part of Application Ser. No. 09/476,643, filed on Dec. 31, 1999, now U.S. Pat. No. 6,177,077, which is a continuation-in-part of Application Serial No. 09/275,070, filed on Mar. 23, 1999, now U.S. Pat. No. 6,015,557, which is a continuation-in-part of Application Serial No. 09/256,388, filed on Feb. 24, 1999, now abandoned."

21. Exhibit 27 is an original U.S. inventor declaration signed April 20, 2001 by Dr. Edward L. Tobinick.

22. Application 09/841,844 issued as U.S. 6,537,549..

23. Exhibit 27, page 2 is a printout of columns 1 and 2 of U.S. 6,537,549, showing that the first sentence of the specification recites "This is a continuation-in-part of application Ser. No. 09/826,976, filed on Apr. 5, 2001, now U.S. Pat. No. 6,419,944, which is a continuation-in-part of application Ser. No. 09/563,651, filed on May 2, 2000, was [*sic*, now] U.S. Pat. No. 6,471,961, which is a continuation-in-part of Application Ser. No. 09/476,643, filed on Dec. 31, 1999, now U.S. Pat. No. 6,177,077, which is a continuation-in-part of application Ser. No. 09/275,070, filed on Mar. 23, 1999, now U.S. Pat. No. 6,015,557, which is a continuation-in-part of application Ser. No. 09/256,388, filed on Feb. 24, 1999, now abandoned."

24. **The foregoing facts show that the USPTO records show that application 09/841,844 is a CIP of 09/826,976.**

C. USPTO RECORDS SHOWING THE BENEFIT CLAIM IN 09/826,976

25. Exhibit 17 is a copy of the 1 page transmittal letter, and page 1 of the specification filed on 04/05/2001 in application 09/826,976. The upper left hand corner of Exhibit 17 has a USPTO date stamp showing "04/05/01." The upper right hand corner shows the USPTO application number "09/826,976."

26. Exhibit 17, page 2 shows the original first sentence of the specification along with the examiner's handwritten amendment dated 03/22/02 revising the priority claim to recite "This is a continuation-in-part of application Ser. No. 09/563,651, filed on May 2, 2000, which is a continuation-in-part of Application Ser. No. 09/476,643, filed on Dec. 31, 1999, now U.S. Pat. No. 6,177,077, which is a continuation-in-part of application Ser. No. 09/275,070, filed on Mar.

23, 1999, now U.S. Pat. No. 6,015,557, which is a continuation-in-part of application Ser. No. 09/256,388, filed on Feb. 24, 1999, now abandoned."

27. Exhibit 18 is an original U.S. inventor declaration signed April 4, 2001, by Edward L. Tobinick.

28. Application 09/826,976 issued as U.S. 6,419,944.

29. Exhibit 19, page 2 is a printout of columns 1 and 2 of U.S. 6,419,944, showing that the first sentence of the specification recites "This is a continuation-in-part of application Ser. No. 09/563,651, filed on May 2, 2000, which is a continuation-in-part of Application Ser. No. 09/476,643, filed on Dec. 31, 1999, now U.S. Pat. No. 6,177,077, which is a continuation-in-part of application Ser. No. 09/275,070, filed on Mar. 23, 1999, now U.S. Pat. No. 6,015,557, which is a continuation-in-part of application Ser. No. 09/256,388, filed on Feb. 24, 1999, now abandoned."

30. Exhibit 19, pages 3 - 5 are the claims in U.S. 6,419,944. Claims 1 - 23 and 30 - 38 relate to methods for inhibiting the action of TNF for treating various medical conditions by administering a TNF antagonist.

31. Exhibit 20 is pages 1-29 from the specification of application 09/666,068 as filed, which contains a description of the invention of claims 1 - 23 and 30 - 38 in U.S. 6,419,944, and, therefore, application 09/666,068 should be added to the priority chain of the subject application.

32. **The foregoing facts show that the USPTO records show that application 09/826,976 is a CIP of 09/476,643 and a CIP of 09/666,068.**

D. USPTO RECORDS SHOWING THE BENEFIT CLAIM IN 09/563,651

33. **Exhibit 20**, page 1 is a copy of the transmittal letter, and first page of the specification filed on 05/02/2000 in application 09/563,651. The upper left hand corner of Exhibit 20 has a USPTO date stamp showing "05/02/00" The upper right hand corner shows the USPTO application number "09/563,651."

34. Exhibit 20, page 2 shows the original first sentence of the specification, whic does not include a priority claim.

35. Exhibit 21 is a copy of the original U.S. inventor declaration filed with application 09/563,651, signed May 2, 2000, and claiming benefit to application co-pending application

09/476,643, filed December 31, 1999.

36. Exhibit 22 is a request for Certificate of Correction, filed December 23, 2005, adding a priority claim as follows: "This application is a continuation-in-part of application Ser. No. 09/476,643, filed Dec. 31, 1999, now U.S. Pat No. 6,177,077, which is a continuation-in-part of Serial No. 09/275,070, filed March 23, 1999, now U.S. Pat No. 6,015,557, which is a continuation-in-part of application Ser. No. 09/256,388, filed on Feb. 24, 1999, now abandoned."

37. Exhibit 23 is an SPE Response for Certificate of Correction dated March 6, 2006, approving the requested filed December 23, 2005.

38. Exhibit 24 is the Certificate of Correction in U.S. 6,471,961, issued May 23, 2006, showing that the first sentence of the specification recites "This application is a continuation-in-part of Application Ser. No. 09/476,643, filed on Dec. 31, 1999, now U.S. Pat. No. 6,177,077, which is a continuation-in-part of application Ser. No. 09/275,070, filed on Mar. 23, 1999, now U.S. Pat. No. 6,015,557, which is a continuation-in-part of application Ser. No. 09/256,388, filed on Feb. 24, 1999, now abandoned."

39. **The foregoing facts show that the USPTO records show that application 09/563,651 is a CIP of 09/476,643.**

E. USPTO RECORDS SHOWING THE BENEFIT CLAIM IN 09/666,068

40 Exhibit 1 is a copy of the 2 page transmittal letter, and page 1 of the specification filed on 09/19/2000 in application 09/666,068. The upper left hand corner of Exhibit 1 has a USPTO date stamp showing "09/19/00" The upper right hand corner shows the USPTO application number "09/666,068."

41 Exhibit 1, pages 1 and 2, indicate that 09/666,068 was filed as a Rule 60 divisional incorporating the prior specification and inventor declaration. Item 8 is checked, and amends the specification before the first line to recite "division of application number 09/476,643, filed Dec. 31, 1999."

42. Exhibit 1 page 3 shows the original first sentence of the specification, i.e., "This is a continuation-in-part of application Serial No. 09/256,388, filed on February 24, 1999" along with the Examiner's handwritten amendment dated 11/15/2001, revising the priority claim to recite "This application is a divisional of Ser. No. 09/476,643, filed Dec. 31, 1999, now U.S.

Pat No. 6,177,077, which is a continuation-in-part of Application Ser. No. 09/256,388, filed on Feb. 24, 1999, now abandoned." (marked-up)

43. Exhibit 2, pages 1 and 2 shows the applicant filed a copy of the original U.S. inventor declaration from 09/476,643, signed by Edward L. Tobinick, M.D. on December 29, 1999, and relied upon that copy to secure the December 11, 2000 filing date.

44. Exhibit 2, page 3 shows applicant requested a correction of filing receipt, dated-stamped "12/06/2000," in stating erroneously: "THIS APPLICATION IS A DIV OF 09/476,643, DATED 12/31/1999, WHICH IS A CIP OF 09/256,388, DATED 2/24/1999, ABANDONED."

45. Exhibit 3, pages 3 - 4 show a two page transmittal letter, date-stamped "Dec 11, 2000" filed in response to the Notice to File Missing Parts, listing "A copy of the Declaration from the parent application (U.S. Serial No. 09/476,643)".

46. Exhibit 3, pages 1 is a Official Filing Receipt mailed "01/24/2001." Exhibit 3, page 2 is an Official Filing Receipt mailed "02/22/2001."

47. Application 09/666,068 issued as US 6,379,666.

48. Exhibit 4 is a printout of the first two columns of US 6,379,666.

49. Exhibit 4 shows that the first sentence of USP 6,379,666 recites "This application is a divisional of Ser. No. 09/476,643, filed Dec. 31, 1999, now U.S. Pat No. 6,177,077, which is a continuation-in-part of application Ser. No. 09/256,388, filed on Feb. 24, 1999, now abandoned."

50. **The foregoing facts show that the USPTO records show that application 09/666,068 is a divisional of 09/476,643.**

F. USPTO RECORDS SHOWING THE BENEFIT CLAIM IN 09/476,643

51 Exhibit 5, pages 1 and 2 shows the original inventor declaration from application 09/476,643, signed by Edward L. Tobinick, M.D., on December 29, 1999. Exhibit 5, page 3 is the first page of the PTO file history for application 09/476,643, stating in the examiner's handwriting verification that "THIS APPLN is a CIP OF 09/275,070 03/23/99 PAT 6,015,557 WHICH IS A CIP OF 09/256,388 02/24/99 ABN"

52. Exhibit 6, page 1 is a one page transmittal letter dated "December 31, 1999 BY EXPRESS MAIL" for a new application showing the filing of an original inventor's declaration. At the upper left is the date "12/31/99" and at the upper right is the serial number "09/476643".

Exhibit 6, page 2 shows the first page of the specification, which one can see originally said "This is a continuation-in-part of Application Serial No. 09/256,388, filed on February 24, 19990." This sentence was crossed-out by the examiner.

53. Exhibit 7, page 1 is the first page of the PTO File History, amended in handwriting by the examiner to state "This Appln is a CIP OF 09/275,070 PAT #6,015,557 WHICH IS A CIP OF 09/256,388 02/24/99 ABN." Exhibit 7, page 2 is another copy of the one page transmittal letter dated "December 31, 1999 BY EXPRESS MAIL" for a new application showing the filing of an original inventor's declaration. At the upper left is the date "12/31/99" and at the upper right is the serial number "09/476643". Exhibit 7, page 3 is an inventor declaration filed with the application. Exhibit 7, page 4 shows the first page of the specification as filed, which stated "This is a continuation-in-part of Application Serial No. 09/256,388, filed on February 24, 19990". This sentence was later crossed-out by the examiner.

54 Exhibit 8, page 1 is a Terminal Disclaimer over US 6,015,557, and page 2 is an original inventor declaration claiming benefit of application "09/275,070 March 23, 1999 U.S. Patent No. 6,015,557" and "09/256,388 February 24, 1999 Abandoned"

55 Exhibit 9, page 2 shows the handwritten amendment by the examiner, dated 8/24/2000 changing the first sentence of the specification to recite ""This application is a continuation-in-part of Application Serial No. 09/275,070, filed on March 23, 1999, now U.S. Patent 6,015,557, which is a continuation-in-part of Application Ser. No. 09/256,388, filed on February 24, 1999, now abandoned"

56. Exhibit 10 is a printout of the first two columns of US 6,177,077, stating in the first paragraph that "This application is a continuation-in-part of Application Serial No. 09/275,070, filed on Mar 23, 1999, now U.S. Pat. No. 6,015,557, which is a continuation-in-part of Application Ser. No. 09/256,388, filed on Feb. 24, 1999, now abandoned."

57. **The foregoing facts show that the USPTO records show that application 09/476,643 1s a continuation-in-part of 09/275,070.**

G. USPTO RECORDS SHOWING THE BENEFIT CLAIM IN 09/275,070

58. Exhibit 11, page 1 is a transmittal letter dated "March 23, 1999 BY EXPRESS MAIL." Page 2 is the first page of the specification as filed.. Pages 3 and 4 are a copy of the original

inventor declaration, claiming benefit under 35 USC 120 to "09/256,388 24 February 1999 pending" signed on 3-20-99 by two inventors, Dr. Edward L. Tobinick, and Arthur Jerome Tobinick. Pages 5 -8 are a copy of a Petition to Make Special filed March 23, 1999. At the upper right on page 5 is the serial number "09/257070" and the date "03/23/99".

59. Exhibit 12 is a printout of the first two columns of US 6,015,557, stating in the first paragraph that "This application is a continuation-in-part of Application Ser. No. 09/256,388, filed on Feb. 24, 1999, now abandoned."

60. **The foregoing facts show that the USPTO records show that application 09/275,070 1s a continuation-in-part of 09/256,388.**

H. USPTO RECORDS SHOWING THE FILING DATE OF 09/256,388

61. Exhibit 13, page 3 is a copy of the first page USPTO file history for application 09/256,388, showing "FILING DATE 02/24/99." Pages 1 - 2 show the original inventor declaration, dated February 21, 1999, signed by two inventors, Dr. Edward L. Tobinick, and Arthur Jerome Tobinick. In 09/256,388, inventor "Edward L. Tobinick, M.D." is the same person as "Dr. Edward L. Tobinick" in 09/275,070 (and "Edward L. Tobinick, M.D." in 09/476,643).

62. Exhibit 14 is another copy of the inventor declaration. Page 2 is transmittal letter dated "FEBRUARY 24, 1999 BY EXPRESS MAIL" listing the filing of an inventor declaration, and specification. Page 3 of Exhibit 14 is the first page of the specification as filed.

63 Exhibit 15, pages 1 - 2 is a Notice of Abandonment "mailed 09/27/99." Exhibit 15, page 3 is communication by applicant dated 9/16/99 stating: "Re: S.N. 09/256,388 Applicant hereby abandons the above-identified application in favor of Appln. S.N. 09/275,070, which has been allowed by Examiner Jarvis."

64. **The foregoing show that the USPTO records show that application 09/256,388 was filed on February 24, 1999 and abandoned on Sept. 16, 1999.**

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I. FACTS WHY THE REQUESTED RELIEF IS NOT MOOT

65. Pending Tobinick application 12/714,205 claims priority to the subject application 09/826,976 (US 6,419,944) as follows: "This is a continuation of application Serial No.

11/262,528, filed on Oct. 28, 2005, which is a division of application Ser. No. 10/269,745, filed Oct. 9, 2002, now U.S. Pat. No. 6,982,089, which is a continuation-in-part of application Ser. No. 09/841,844, filed on Apr. 25, 2001, now U.S. Pat. No. 6,537,549, which is a continuation-in-part of **application Ser. No. 09/826,976, filed on Apr. 5, 2001, now U.S. Pat. No. 6,419,944, which is a continuation-in-part of application Ser. No. 09/666,068, filed Dec. 11, 2000, now U.S. Pat. No. 6,379,666, which is a division of application Ser. No. 09/476,643, filed on Dec. 31, 1999, now U.S. Pat. No. 6,177,077,** which is a continuation-in-part of application Ser. No. 09/275,070, filed on Mar. 23, 1999, now U.S. Pat. No. 6,015,557, which is a continuation-in-part of application Ser. No. 09/256,388, filed on Feb. 24, 1999, now abandoned." (emphasis added)

J. FACTS SHOWING THE FAILURE TO PROPERLY CLAIM BENEFIT WAS UNINTENTIONAL

66. The foregoing facts 1 - 65 show that failure to claim in this application priority to 09/666,068 was an unintentional clerical error.

K. FACTS RELATING TO THE LEGAL STANDARD FOR ENTRY OF CORRECTION OF BENEFIT CLAIMS

67. Exhibit 16 is a copy of pages from Section 1481.03 of the current version of the MPEP.

L. RELATED USPTO PROCEEDINGS

68. The applicant is presenting herewith an Amendment to correct benefit in the subject application 09/841,844.

69. The applicant is filing herewith a corresponding request for a Certificate of Correction in the patent that issued from the '844 application, i.e., U.S. Pat. 6,537,549.

III. REASONS WHY THE PETITION SHOULD BE GRANTED

On the merits, the petition should be granted because (1) the relief requested is not moot; (2) an amendment as to benefit in an issued application is submitted herewith, (3) all of the elements required under 37 CFR 1.78(a)(3) have been presented, so awarding a corrected

priority chain in application Ser. No. 09/841,844 is proper, and (4) a request for the appropriate Certificate of Correction has been filed.

A.. STANDARD FOR GRANT OF PETITION

1. FORMAL MATTERS

This petition requests entry of an amendment in an issued application filed after November 29, 2000. Therefore petition under Rule 1.78 is proper.

(CX13 "Eighteen-Month Publication Questions and Answers" http://www.uspto.gov/patents/law/aipa/18month/18monthfaq.jsp#cx)

The applicant is paying the 37 CFR 1.17(t) fee therefore via credit card upon EFS web submission of this petition.

2. THE PETITION IS NOT MOOT

The petition is not moot because, even though 09/841,844 is issued, a pending application claims priority to this application. Fact 65.

3. CRITERIA FOR CORRECTION OF BENEFIT

The amendment that this petition requests entry of corrects benefit. The requirements to obtain benefit and to correct benefit are governed by Rule 1.78. MPEP 1481.03 contains criteria for granting a Certificate of Correction correcting benefit in an issued patent. See the section titled "Correction of 35 U.S.C. 119 and 35 U.S.C. 120 Benefits." In view of the foregoing, this petition shows compliance with the criteria for correction of benefit under Rule 1.78.

B. THE APPLICANT HAS COMPLIED WITH THE CRITERIA FOR CLAIMING BENEFIT TO 09/666,068

1. THE APPLICANT HAS COMPLIED WITH THE REQUIREMENTS OF 37 C.F.R. 1.78

The following paragraphs in this subsection identify requirements in Rule 1.78 for

claiming priority, and show compliance with those requirements.

37 CFR 1.78(a)(1) authorizes a claim to priority to prior filed applications only if the applications name at least one common inventor and disclose the claimed invention. The prior filed application is 09/666,068. The common inventor is Edward L. Tobinick, Facts 19-50.

37 CFR 1.78(a)(1)(i) and (ii) require the prior filed applications to be either international applications or applications entitled to a filing date. The prior filed application is 09/666,068, which was entitled to and accorded a filing date. Exhibit 1, Facts 40 - 50.

37 CFR 1.78(a)(2)(i) requires a claim to priority to be present or amended to be present during the pendency of the application, unless the application was filed prior to November 29, 2000, and to state the relationship between the applications. This application is an application filed under 111(a) after November 29, 2000. Accordingly, the amendment submitted herewith provides the specific references and relationship to 09/666,068, which is a divisional of application Ser. No. 09/476,643, which is a continuation-in-part of 09/275,070, which is a continuation-in-part of 09/256,388.

37 CFR 1.78(a)(2)(iii) requires the claim to priority be presented in an application data sheet or amendment to the first sentence of the specification following the title. The amendment submitted herewith provides the claim to priority to 09/666,068 in the first sentence of the specification following the title.

37 CFR 1.78(a)(3) authorizes an amendment claiming priority after the time periods specified by 1.78(a)(2)(ii) only if the late filing of the claim the priority was unintentionally delayed. The entire delay between the date the priority claim was due under paragraph 37 CFR 1.78 (a)(2)(ii) and the date of submission of this Petition was unintentional. Fact 57.

37 CFR 1.78 contains no other requirements applicable to grant of this petition. In view of the foregoing, this petition should be granted.

DATE: 6-10-2010 **SIGNATURE**: /RobertHahl#33,893/

PRINTED NAME: Robert W. Hahl, Ph.D.

Date/time code: June 10, 2010 (1:50pm)

Y:\Clients\TACT\TACT0019\PetitionToCorrectPriority_6537549.wpd

**> PTO/SB/13 (11-96)
Approved for use through 6/30/99. OMB 0651-0033
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REQUEST FOR FILING A PATENT APPLICATION UNDER 37 CFR 1.60

DOCKET NUMBER	ANTICIPATED CLASSIFICATION OF THIS APPLICATION		PRIOR APPLICATION EXAMINER	ART UNIT
	CLASS	SUBCLASS		
TOBINICK 3.0-009(CIP)(DIVII			Examiner William R.A. Jarvis	1614

Address to:
Assistant Commissioner for Patents
Washington, D.C. 20231

This is a request for filing a ☐ continuation ☒ divisional application under 37 CFR 1.60, of pending prior Application Number 09 / 476,643, filed on 12/31/99 entitled TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS

1. Enclosed is a copy of the latest inventor-signed prior application, including a copy of the oath or declaration showing the original signature or an indication it was signed. I hereby verify that the papers are a true copy of the latest signed prior application number 09 / 476,643, and further that all statements made herein of my own knowledge are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

CLAIMS	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
	TOTAL CLAIMS (37 CFR 1.16(c))	17 - 20 =	--	x $_____ =	$ --
	INDEPENDENT CLAIMS (37 CFR 1.16(b))	1 - 3 =	--	x $_____ =	--
	MULTIPLE DEPENDENT CLAIMS (if applicable) (37 CFR 1.16(d))			+ $_____ =	
			BASIC FEE (37 CFR 1.16(a))		+ $345.00
			Total of above Calculations =		
			Reduction by 50% for filing by small entity (Note 37 CFR 1.9, 1.27, 1.28).		
			TOTAL =		$345.00

2. ☐ A verified statement to establish small entity status under 37 CFR 1.9 and 1.27
   ☐ is enclosed.
   ☒ was filed in prior application number 09 / 476,643 and such status is still proper and desired (37 CFR 1.28(a)).
3. ☐ The Commissioner is hereby authorized to charge any fees which may be required under 37 CFR 1.16 and 1.17, or credit any overpayment to Deposit Account No. _____. A duplicate copy of this sheet is enclosed.
4. ☒ A check in the amount of $ 345 is enclosed.
5. ☒ Cancel in this application original claims 1-49 & 66-99 of the prior application before calculating the filing fee. (At least one original independent claim must be retained for filing purposes.)
6. ☒ The inventor(s) of the invention being claimed in this application is (are):
   Dr. Edward L. Tobinick
7. ☐ This application is being filed by less than all the inventors named in the prior application. In accordance with 37 CFR 1.60(b), the Commissioner is requested to delete the name(s) of the following person or persons who are not inventors of the invention being claimed in this application:
8. ☒ Amend the specification by inserting before the first line the sentence: "This application is a ☐ continuation ☒ division of application number 09 / 476,643, filed Dec. 31, 1999, (status, abandoned, pending, etc.)."

[Page 1 of 2]

Burden Hour Statement: This form is estimated to take 0.5 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

**> PTO/SB/13 (11-96)
Approved for use through 5/30/99. OMB 0651-0033
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

(REQUEST FOR FILING A PATENT APPLICATION UNDER 37 CFR 1.60, PAGE 2)

9. ☐ New formal drawings are enclosed.

10. ☐ Priority of foreign application number _____, filed on _____ in _____ is claimed under 35 U.S.C. 119(a) - (d).
☐ The certified copy has been filed in prior application number ___ / _____, filed _____.

11. ☒ A preliminary amendment is enclosed.

12. ☐ The prior application is assigned of record to _____

13. ☐ Also enclosed:

14. ☒ The power of attorney in the prior application is to: EZRA SUTTON, P.A.
Plaza 9, 900 Route 9
Woodbridge, New Jersey 07095.

a. ☒ The power of attorney appears in the original papers in the prior application.

b. ☐ Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.

c. ☐ Address all future correspondence to: (May only be completed by applicant, or attorney or agent of record.)

☐ Customer Number _____ → *Place Customer Number Bar Code Label here*
Type Customer Number here
OR
☒ Firm or Individual Name EZRA SUTTON, P.A.
Address Plaza 9, 900 Route 9
Address
City Woodbridge, State New Jersey ZIP 07095
Country
Telephone (732) 634-3520 Fax (732) 634-3511

9-5-00
Date

Signature
EZRA SUTTON
Typed or printed name

☐ Inventor(s)
☐ Assignee of complete interest. Certification under 37 CFR 3.73(b) is enclosed.
☒ Attorney or agent of record
☐ Filed under 37 CFR 1.34(a)
Registration number if acting under 37 CFR 1.34(a). 25,770

[Page 2 of 2]

TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS

RELATED APPLICATION

application is a divisional of 09/476,643, filed December 31, 1999, now U.S. Patent 6,177,077, which

This is a continuation-in-part of Application Serial No. 09/256,388, filed on February 24, 1999, now abandoned.

11/15/01

FIELD OF THE INVENTION

The present invention relates to tumor necrosis factor (TNF) antagonists or TNF blockers for the treatment of neurological disorders, trauma, injuries or compression; demyelinating neurological disorders, including multiple sclerosis; neurodegenerative diseases, including Alzheimer's disease; muscular disorders; and disorders of the optic nerve and retina (hereinafter "Neurologic and Related TNF Disorders"). More particularly, the TNF antagonists, TNF inhibitors or TNF blockers, are used for the treatment, prevention or amelioration of these "Neurologic and Related TNF Disorders" by modulating the action of TNF in the human body. The use of these TNF antagonists or TNF blockers results in the amelioration of these disorders and diseases and represents a novel use for this class of drugs.

BACKGROUND OF THE INVENTION

Neurological disorders due to demyelinating disease (e.g. multiple sclerosis), immune disease, inflammation, trauma, or compression, occur in different clinical forms depending upon the anatomic site and the cause and natural history of the physiological problem. For example, in Alzheimer's disease the brain undergoes a serious form of neurodegeneration

Exhibit 2_Pages41-45fromIFW_09666068_666.

Applicant or Patentee: Edward L. TOBINICK M.D. Attorney's
Serial or Patent No.: Docket No.:
Filed or Issued:
Title: TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.2(f) AND 1.27(b) - INDEPENDENT INVENTOR

As a below-named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, to the Patent and Trademark office with regard to the invention entitled TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS described in:

[X] the specification filed herewith
[ ] Application Serial No. _____, filed _____
[ ] Patent No. _____, issued _____.

I have not assigned, granted, conveyed, or licensed and am under no obligation, under contract or law to assign, grant, convey, or license, any rights in the invention to any person who could not be classified as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern, or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

[X] no such person, concern, or organization
[ ] persons, concerns, or organizations listed below*

*NOTE: Separate verified statements are required from each named person, concern, or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

FULL NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

FULL NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

FULL NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Edward L. TOBINICK, M.D.		
NAME OF INVENTOR	NAME OF INVENTOR	NAME OF INVENTOR
X Edward L. Tobinick M.D.		
Signature of Inventor	Signature of Inventor	Signature of Inventor
December 29, 1999		
Date	Date	Date

DECLARATION FOR PATENT APPLICATION

Docket No. TOBINICK 3.0-009(CIP)

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS, the specification of which

(check one) ☒ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Ezra Sutton, Reg. No. 25,770

Address all telephone calls to _____ at telephone no. (732) 634-3520

Address all correspondence to EZRA SUTTON, P.A.
Plaza 9, 900 Route 9
Woodbridge, New Jersey 07095

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor Edward L. TOBINICK, M.D.

Inventor's signature X Edward L. Tobinick M.D. Date December 29, 1999

Residence Los Angeles, California 90024-6903 Citizenship United States of America

Post Office Address 100 UCLA Medical Plaza, Suite 205
Los Angeles, California 90024-6903

Full name of second joint inventor, if any _____

Second Inventor's signature _____ Date _____

Residence _____ Citizenship _____

Post Office Address _____

(Supply similar information and signature for third and subsequent joint inventors.)

#5 3P 2/26/01

OIPE DEC 06 2000 PATENT & TRADEMARK OFFICE

RECEIPT

RECEIVED FEB 13 2001 TECH CENTER 1600/2900

TOBINICK 3.0-009 (CIP)(DIV I)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BY FAX - 1-703-308-7751

In re patent application of: EDWARD L. TOBINICK, M.D.	:	
Serial No. 09/666,068	:	Group Art Unit 1614
Filed: September 19, 2000	:	Examiner
For: TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS	:	December 6, 2000

RECEIVED JAN 12 2001 OIPE/JCW'S

Assistant Commissioner for Patents
Washington, D.C. 20231

CORRECTION OF FILING RECEIPT

Sir:

Please issue a corrected filing receipt, and correct the following data:

THIS APPLICATION IS A DIV OF 09/476,643, DATED 12/31/1999, WHICH IS A CIP OF 09/256,388, DATED 2/24/1999, ABANDONED.

See the enclosed filing receipt.

Respectfully submitted,

EZRA SUTTON, P.A.

Ezra Sutton

EZRA SUTTON
Reg. No. 25,770

Plaza 9, 900 Route 9
Woodbridge, New Jersey 07095
(732) 634-3520
ES/jmt

UNITED STATES PATENT AND TRADEMARK CI

FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
09/19/2000	1614	345	TOBINICK 3.0-009	21	2	

09/66[illegible]

OIPE SC1130 DEC 0 6 2000 PATENT & TRADEMARK OFFICE

Ezra Sutton PA
Plaza 9 900 Route 9
Woodbridge, NJ 07095

Date Mailed: 11/15/2000

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the PTO processes the reply to the Notice, the PTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

RECEIVED
FEB 13 2001
TECH CENTER 1600/2900

Applicant(s)
Edward L. Tobinick, Los Angeles, CA ;

Continuing Data as Claimed by Applicant
THIS APPLICATION IS A CIP OF 09/256,388 02/24/1999 ABN

Foreign Applications

If Required, Foreign Filing License Granted 11/15/2000

**** SMALL ENTITY ****

Title
TNF inhibitors for the treatment of neurological, retinal and muscular disorders

Preliminary Class
514

Data entry by : HINES, BRENDA **Team :** OIPE **Date:** 11/15/2000

RECEIVED
DEC 11 2000
EZRA SUTTON P.A.

FILE COPY

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

Bib Data Sheet

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
09/666,068	12/11/2000 RULE _	514	1614	TOBINICK3.0-009 (CIP)(DIVI

APPLICANTS

Edward L. Tobinick, Los Angeles, CA ;

**** CONTINUING DATA ***************************

THIS APPLICATION IS A DIV OF 09/476,643 12/31/1999 PAT 6,177,077
WHICH IS A CIP OF 09/256,388 02/24/1999 ABN

**** FOREIGN APPLICATIONS *********************

IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 11/02/2000

** SMALL ENTITY **

		STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
Foreign Priority claimed	☐ yes ☒ no	CA	_	16	1
35 USC 119 (a-d) conditions met	☐ yes ☒ no ☐ Met after Allowance				
Verified and Acknowledged	Examiner's Signature Initials				

ADDRESS

_

EZRA SUTTON, P.A.
Plaza 9, 900 Route 9
Woodbridge ,NJ 07095

TITLE

TNF inhibitors for the treatment of neurological, retinal and muscular disorders

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
410	No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Exhibit 3_Pages 34-39fromIFW_09666068_666.pdf

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
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APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
09/666,068	12/11/2000	1614	410	TOBINICK3.0-009(CIP)(DIV)I	16	1	

CORRECTED FILING RECEIPT

OC000000005701748

EZRA SUTTON, P.A.
Plaza 9, 900 Route 9
Woodbridge, NJ 07095

Date Mailed: 01/24/2001

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the PTO processes the reply to the Notice, the PTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Edward L. Tobinick, Los Angeles, CA ;

Continuing Data as Claimed by Applicant

THIS APPLICATION IS A DIV OF 09/476,643 12/31/1999 PAT 6,177,077
WHICH IS A CIP OF 09/256,388 02/24/1999 ABN

Foreign Applications

If Required, Foreign Filing License Granted 11/02/2000

**** SMALL ENTITY ****

Title

TNF inhibitors for the treatment of neurological, retinal and muscular disorders

Preliminary Class

514

Data entry by : BURSE, JANICE **Team :** OIPE **Date:** 01/24/2001

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
09/666,068	12/11/2000	1614	410	TOBINICK3.0-009(CIP)(DIVI		16	1

CONFIRMATION NO. 6420

FILING RECEIPT

OC000000005791231

EZRA SUTTON, P.A.
Plaza 9, 900 Route 9
Woodbridge, NJ 07095

Date Mailed: 02/22/2001

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the PTO processes the reply to the Notice, the PTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Edward L. Tobinick, Los Angeles, CA;

Continuing Data as Claimed by Applicant

THIS APPLICATION IS A DIV OF 09/476,643 12/31/1999 PAT 6,177,077
WHICH IS A CIP OF 09/256,388 02/24/1999 ABN

Foreign Applications

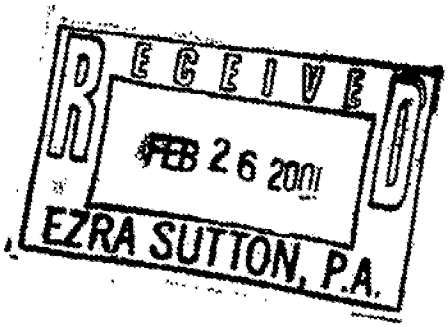
If Required, Foreign Filing License Granted 11/02/2000

Projected Publication Date: 05/31/2001

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****



Title

TNF inhibitors for the treatment of neurological, retinal and muscular disorders

Sector #3

TOBINICK 3.0-009 (CIP)(DIV II)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of: :
EDWARD L. TOBINICK, M.D.

Serial No. 09/666,068 : Group Art Unit 1614

Filed: September 19, 2000 : Examiner

For: TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS : December 6, 2000

Assistant Commissioner for Patents
Washington, D.C. 20231

Attention: Customer Service Center
Initial Patent Examination Division

RESPONSE

Sir:

This is in response to the "Notice to File Missing Parts of Nonprovisional Application," dated November 2, 2000.

Enclosed for filing are the following:

1. Page 54, which was missing from the application;

2. A copy of the Declaration from the parent application (U.S. Serial No. 09/476,643);

3. A copy of the Verified Statement for a Small Entity from the parent application (U.S. Serial No. 09/476,643);

4. The surcharge fee of $65 for a small entity; and

5. A copy of the Notice to File Missing Parts of Nonprovisional Application.

It is requested that this application be given a new filing date upon receipt of this Response.

Respectfully submitted,

EZRA SUTTON, P.A.

EZRA SUTTON, Reg. No. 25,770

Plaza 9, 900 Route 9
Woodbridge, New Jersey 07095

(732) 634-3520

ES/jmt

Enclosures

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST-CLASS MAIL IN AN ENVELOPE ADDRESSED TO:
ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231 ON

Date December 6, 2000

By Judith M. Traina

TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS

RELATED APPLICATION

This application is a divisional of Ser. No. 09/476,643, filed Dec. 31, 1999, now U.S. Pat No. 6,177,077, which is a continuation-in-part of application Ser. No. 09/256,388, filed on Feb. 24, 1999, now abandoned.

FIELD OF THE INVENTION

The present invention relates to tumor necrosis factor (TNF) antagonists or TNF blockers for the treatment of neurological disorders, trauma, injuries or compression; demyelinating neurological disorders, including multiple sclerosis; neurodegenerative diseases, including Alzheimer's disease; muscular disorders; and disorders of the optic nerve and retina (hereinafter "Neurologic and Related TNF Disorders"). More particularly, the TNF antagonists, TNF inhibitors or TNF blockers, are used for the treatment, prevention or amelioration of these "Neurologic and Related TNF Disorders" by modulating the action of TNF in the human body. The use of these TNF antagonists or TNF blockers results in the amelioration of these disorders and diseases and represents a novel use for this class of drugs.

BACKGROUND OF THE INVENTION

Neurological disorders due to demyelinating disease (e.g. multiple sclerosis), immune disease, inflammation, trauma, or compression, occur in different clinical forms depending upon the anatomic site and the cause and natural history of the physiological problem. For example, in Alzheimer's disease the brain undergoes a serious form of neurodegeneration of unknown etiology. Common to all of these disorders is the fact that they can cause permanent neurological damage, that damage can occur rapidly and be irreversible, and that current treatment of these conditions is unsatisfactory, often requiring surgery and/or the use of pharmacologic agents, which are often not completely successful.

These neurological conditions include acute spinal cord trauma, spinal cord compression, spinal cord hematoma, cord contusion (these cases are usually traumatic, such as motorcycle accidents or sports injuries); nerve compression, the most common condition being a herniated disc causing sciatic nerve compression, neuropathy, and pain; but also including cervical disc herniation, causing nerve compression in the neck; acute or chronic spinal cord compression from cancer (this is usually due to metastases to the spine, such as from prostate, breast or lung cancer); autoimmune disease of the nervous system; and demyelinating diseases, the most common condition being multiple sclerosis.

Steroid drugs such as cortisone that are used to treat many of the aforementioned neurological problems and conditions are particularly hazardous because they are used either at high dosage, with a corresponding increasing risk of side effects, or because they are used chronically, also increasing their adverse effects. Lastly, steroids are only partially effective or completely ineffective.

Tumor necrosis factor (TNF), a naturally occurring cytokine, plays a central role in the inflammatory response and in immune injury. TNF is formed by the cleavage of a precursor transmembrane protein, forming soluble molecules which aggregate to form trimolecular complexes. These complexes then bind to receptors found on a variety of cells. Binding produces an array of pro-inflammatory effects, including release of other pro-inflammatory cytokines, including interleukin (IL)-6, IL-8, and IL-1; release of matrix metalloproteinases; and up regulation of the expression of endothelial adhesion molecules, further amplifying the inflammatory and immune cascade by attracting leukocytes into extravascular tissues. TNF is now well established as key in the pathogenesis of rheumatoid arthritis (RA) and Crohn's Disease.

Specific inhibitors of TNF, only recently commercially available, now provide the possibility of therapeutic intervention in TNF mediated diseases. Dramatic therapeutic success has already been demonstrated with infliximab, a chimeric anti-TNF monoclonal antibody (mAb), in treating Crohn's Disease and RA; and with etanercept, a recombinant fusion protein consisting of two soluble TNF receptors joined by the Fc fragment of a human IgG1 molecule, in treating RA and Psoriatic Arthritis. Other specific anti-TNF agents are under development, including D2E7 (a human anti-TNF mAb), CDP 571 (a chimeric, but 95% humanized, anti-TNF mAb), and a pegylated soluble TNF type I receptor. Additionally, thalidomide has been demonstrated to be a potent anti-TNF agent. Further, anti-TNF therapies may include gene therapy and the development of selective inhibitors of the TNF-alpha converting enzyme.

As with other organ systems, TNF has been shown to have a key role in the central nervous system. There is a need for TNF inhibitors that will open a new realm of therapeutic possibilities for a wide variety of neurological and related disorders. These disorders are diverse and include inflammatory and autoimmune disorders of the nervous system, including multiple sclerosis, Guillain Barre syndrome, and myasthenia gravis; degenerative disorders of the nervous system, including Alzheimer's disease, Parkinson's disease and Huntington's disease; disorders of related systems of the retina and of muscle, including optic neuritis, macular degeneration, diabetic retinopathy, dermatomyositis, amyotrophic lateral sclerosis, and muscular dystrophy; and injuries to the nervous system, including traumatic brain injury, acute spinal cord injury, and stroke.

The limited ability of the body to effect repair after injury to the nervous system, the devastating nature of these diseases and the lack of effective therapy all highlight the importance of early therapy aimed at preventing or limiting neuronal destruction. Anti-TNF therapies are ideally suited to this task because they have been demonstrated to dramatically limit inflammation by interrupting the inflammatory cascade at a fundamental level.

There remains a need for a new pharmacologic treatment of these aforementioned physiological problems of the nervous system associated with autoimmune disease, demyelinating diseases, neurodegenerative diseases, trauma, injuries and compression with the pharmacological use of TNF antagonists or TNF blockers, which are greatly beneficial for the large number of patients whom these conditions affect. Drugs which are powerful TNF blockers are etanercept, infliximab, pegylated soluble TNF Receptor Type I (PEGs TNF-RI), other agents containing soluble TNF receptors, CDP571 (a humanized monoclonal anti-TNF-alpha antibodies), thalidomide, phosphodiesterase 4 (IV) inhibitor thalidomide analogues and other phosphodiesterase IV inhibitors. Etanercept or infliximab may be used for the immediate, short term and long term (acute and chronic) blockade of TNF in order to minimize neurological damage mediated by TNF dependent processes occurring in the aforementioned neurological disorders. The use of these TNF antagonists or TNF blockers would result in the amelioration of these physiological neurological problems.

DECLARATION FOR PATENT APPLICATION

Docket No. TOBINICK 3.0-009(CIP)

As a below named inventor, I hereby declare that: Exhibit S Pages170-172fromIFW 09476643 077.pdf

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS, the specification of which

(check one) ☒ is attached hereto.

☐ was filed on _____ as Application Serial No. _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Ezra Sutton, Reg. No. 25,770

Address all telephone calls to _____ at telephone no. (732) 634-3520

Address all correspondence to EZRA SUTTON, P.A.
Plaza 9, 900 Route 9
Woodbridge, New Jersey 07095

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor: Edward L. TOBINICK, M.D.

Inventor's signature X Edward L. Tobinick M.D. Date December 29, 1999

Residence Los Angeles, California 90024-6903 Citizenship United States of America

Post Office Address 100 UCLA Medical Plaza, Suite 205
Los Angeles, California 90024-6903

Full name of second joint inventor, if any _____

Second Inventor's signature _____ Date _____

Residence _____ Citizenship _____

Post Office Address _____

(Supply similar information and signature for third and subsequent joint inventors.)

Applicant or Patentee: Edward L. TOBINICK, M.D. Attorney's
Serial or Patent No.: Docket No.:
Filed or Issued:
Title: TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.2(f) AND 1.27(b) - INDEPENDENT INVENTOR

As a below-named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, Untied States Code, to the Patent and Trademark office with regard to the invention entitled TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS described in:

[X] the specification filed herewith
[ ] Application Serial No. _____, filed _____
[ ] Patent No. _____, issued _____.

I have not assigned, granted, conveyed, or licensed and am under no obligation, under contract or law to assign, grant, convey, or license, any rights in the invention to any person who could not be classified as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern, or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

[X] no such person, concern, or organization
[ ] persons, concerns, or organizations listed below*

*NOTE: Separate verified statements are required from each named person, concern, or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

FULL NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

FULL NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

FULL NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Edward L. TOBINICK, M.D.		
NAME OF INVENTOR	NAME OF INVENTOR	NAME OF INVENTOR
X		
Signature of Inventor	Signature of Inventor	Signature of Inventor
December 29, 1999		
Date	Date	Date

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
09/476,643	12/31/99	~~435~~ 514	~~1618~~ 1614	TOBINICK.3.0

APPLICANT

EDWARD L. TOBINICK, LOS ANGELES, CA.

CONTINUING DOMESTIC DATA********
VERIFIED asj THIS APPLN IS A CIP OF 09/275,070 03/23/99 PAT 6,015,557
WHICH IS A CIP OF 09/256,388 02/24/99 ABN

371 (NAT'L STAGE) DATA********
VERIFIED asj NONE

FOREIGN APPLICATIONS********
VERIFIED asj NONE

IF REQUIRED, FOREIGN FILING LICENSE GRANTED 02/07/00 ** SMALL ENTITY **

Foreign Priority claimed 35 USC 119 (a-d) conditions met	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐yes ☒no ☐yes ☒no ☐Met after Allowance Verified and Acknowledged asj Examiner's Initials _____ Initials	CA	0	99	8

ADDRESS

EZRA SUTTON PA
PLAZA 9 900 ROUTE 9
WOODBRIDGE NJ 07095

TITLE

TNT INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL ~~RETINAL AND MUSCULAR~~ DISORDERS

asj 8/24/00

FILING FEE RECEIVED	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT NO. _____ for the following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit
$501		

01-05-00

A

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PLAZA 9
900 ROUTE 9
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EZRA SUTTON*
OF COUNSEL
ROBERT A. GREEN
DAVID L. DAVIS

*MEMBER OF N.J. AND N.Y. BARS

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CABLE: TRADEPAT
FAX: (732) 634-3511

December 31, 1999

BY EXPRESS MAIL

Assistant Commissioner for Patents
Washington, D.C. 20231

File No.: TOBINICK 3.0-009 (CIP)
Inventor(s): Edward L. TOBINICK
Title: TNFIINHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS

Assignee: None

Dear Sir:

Enclosed herewith are the following documents in the above-identified application for a Letters Patent of the United States:

2 Pages of Abstract
29 Pages of Specification
99 Number of Claims
- Sheets of Drawings
- Assignment for Recording (attached to copy of this letter)
X PETITION TO MAKE SPECIAL; LIST OF PRIOR ART CITED BY APPLICANT; 5 PRIOR ART PATENTS; FEE OF $130
X Verified Statement for Small Entity Status
Declaration, Power of Attorney & Petition
Two (2) return-addressed postcards
(PLEASE PROVIDE FILING DATE & SERIAL NUMBER)

Check No. 3884 in the amount of $510 ($380 + $130), calculated as follows:

Basic Fee (**Large Business $760.00) (*Small Business $380.00)	$ 380
Additional Fees:	
Total number of claims 99	
Total number of claims in excess of 20, 79 times (**$18)(*$9)	711
Number of independent claims 8	
Number of independent claims minus 3, 5 times (**$78)(*$39)	195
Assignment recording fee ($40)	
Multiple dependent claims (**$260) (*$130)	
	$1,286
PETITION TO MAKE SPECIAL	130
TOTAL filing and assignment recording fees	$1,416

CONVENTION DATE _____ for _____ Appln. No. _____ is claimed.

Priority Document: ____Enclosed ____Will follow

Respectfully submitted,

EZRA SUTTON, Reg No. 25,770

ES/jmt
Enclosures

TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS

RELATED APPLICATION

This is a continuation-in-part of Application Serial No. 09/256,388, filed on February 24, 1999.

FIELD OF THE INVENTION

The present invention relates to tumor necrosis factor (TNF) antagonists or TNF blockers for the treatment of neurological disorders, trauma, injuries or compression; demyelinating neurological disorders, including multiple sclerosis; neurodegenerative diseases, including Alzheimer's disease; muscular disorders; and disorders of the optic nerve and retina (hereinafter "Neurologic and Related TNF Disorders"). More particularly, the TNF antagonists, TNF inhibitors or TNF blockers, are used for the treatment, prevention or amelioration of these "Neurologic and Related TNF Disorders" by modulating the action of TNF in the human body. The use of these TNF antagonists or TNF blockers results in the amelioration of these disorders and diseases and represents a novel use for this class of drugs.

BACKGROUND OF THE INVENTION

Neurological disorders due to demyelinating disease (e.g. multiple sclerosis), immune disease, inflammation, trauma, or compression, occur in different clinical forms depending upon the anatomic site and the cause and natural history of the physiological problem. For example, in Alzheimer's disease the brain undergoes a serious form of neurodegeneration

FILE COPY

Bib Data Sheet

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
09/476,643	12/31/1999 RULE _	514	1614	TOBINICK.3.0

APPLICANTS
EDWARD L. TOBINICK, LOS ANGELES, CA ;

This Appln is a CIP of 9/275,070 PAT # 6,015,557

** CONTINUING DATA ********** WHICH ~~THIS APPLICATION~~ IS A CIP OF 09/256,388 02/24/1999 ABN

RECEIVED
MAR 27 2000
TECH CENTER 1600/2900

** FOREIGN APPLICATIONS **********

IF REQUIRED, FOREIGN FILING LICENCE GRANTED ** SMALL ENTITY **
** 02/07/2000

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☑ no	CA	_	99	8
35 USC 119 (a-d) conditions met ☐ yes ☑ no ☐ Met after Allowance				
Verified and Acknowledged Examiner's Signature _____ Initials				

ADDRESS

EZRA SUTTON PA
PLAZA 9 900 ROUTE 9
WOODBRIDGE, NJ 07095

TITLE

8/24/00

TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, ~~RETINAL AND MUSCULAR~~ DISORDERS

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
510	No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

01-05-00

A

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EZRA SUTTON*
OF COUNSEL
ROBERT A. GREEN
DAVID L. DAVIS

*MEMBER OF N.J. AND N.Y. BARS

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December 31, 1999

BY EXPRESS MAIL

Assistant Commissioner for Patents
Washington, D.C. 20231

File No.: TOBINICK 3.0-009 (CIP)
Inventor(s): Edward L. TOBINICK
Title: TNFI INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS

Assignee: None

Dear Sir:

Enclosed herewith are the following documents in the above-identified application for a Letters Patent of the United States:

2 Pages of Abstract
29 Pages of Specification
99 Number of Claims
- Sheets of Drawings
- Assignment for Recording (attached to copy of this letter)
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X Verified Statement for Small Entity Status
Declaration, Power of Attorney & Petition
Two (2) return-addressed postcards
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TOTAL filing and assignment recording fees	$1,416

CONVENTION DATE _____ for _____ Appln. No. _____ is claimed.

Priority Document: ____Enclosed ____Will follow

Respectfully submitted,

EZRA SUTTON, Reg No. 25,770

ES/jmt
Enclosures

Applicant or Patentee: Edward L. TOBINICK, M.D. Attorney's
Serial or Patent No.: Docket No.:
Filed or Issued:
Title: TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.2(f) AND 1.27(b) - INDEPENDENT INVENTOR

As a below-named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, Untied States Code, to the Patent and Trademark office with regard to the invention entitled TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS described in:

[X] the specification filed herewith
[ ] Application Serial No. _____, filed _____
[ ] Patent No. _____, issued _____.

I have not assigned, granted, conveyed, or licensed and am under no obligation, under contract or law to assign, grant, convey, or license, any rights in the invention to any person who could not be classified as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern, or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

[X] no such person, concern, or organization
[ ] persons, concerns, or organizations listed below*

*NOTE: Separate verified statements are required from each named person, concern, or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

FULL NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

FULL NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

FULL NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Edward L. TOBINICK, M.D.		
NAME OF INVENTOR	NAME OF INVENTOR	NAME OF INVENTOR
X Edward L. Tobinick MD		
Signature of Inventor	Signature of Inventor	Signature of Inventor
December 29, 1999		
Date	Date	Date

TOBINICK 3.0-009 (CIP)

TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS

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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT

Docket Number (Optional): TOBINICK 3.0-009 (CIP)

In re Application of: EDWARD L. TOBINICK
Application No.: 09/476,643
Filed: December 31, 1999
For: TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL RETINAL AND MUSCULAR DISORDERS

The owner*, EDWARD L. TOBINICK of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent No. 6,015,557. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney of record.

Signature — July 20, 2000 (Date)

EZRA SUTTON
Typed or printed name

☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

*Certification under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

DECLARATION FOR PATENT APPLICATION

Docket No. TOBINICK 3.0-009(CIP)

OFFICIAL

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS, the specification of which

(check one) ☒ is attached hereto.

☐ was filed on _____ as Application Serial No. _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

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I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)
09/256,388	February 24, 1999	Abandoned
09/275,070	March 23, 1999	U.S. Patent No. 6,015,557

(Application Serial No.) (Filing Date) (Status—patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Ezra Sutton, Reg. No. 25,770

Address all telephone calls to _____ at telephone no. (732) 634-3520

Address all correspondence to EZRA SUTTON, P.A.
Plaza 9, 900 Route 9
Woodbridge, New Jersey 07095

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor Edward G. Tobinick, M.D.

Inventor's signature _____ Date July 19, 2000

Residence Los Angeles, California Citizenship United States of America

Post Office Address 100 UCLA Medical Plaza, Suite 205
Los Angeles, California 90024-6903

Full name of second joint inventor, if any _____

Second Inventor's signature _____ Date _____

Residence _____ Citizenship _____

Post Office Address _____

(Supply similar information and signature for third and subsequent joint inventors.)

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Date 7/20/00

OFFICIAL

TO: EXR JARVIS

FAX NO. 703-308-4556

FROM: EZRA SUTTON

FAX NO. 1-732-634-3511
PHONE: 1-732-634-3520

TOTAL NUMBER OF PAGES: 8

Amendment Enclosed.

TOBINICK 3.0-009 (CIP)

OFFICIAL

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BY FAX AND MAIL

In re patent application of:
EDWARD L. TOBINICK

Serial No.: 09/476,643 — Group Art Unit 1614

Filed: December 31, 1999 — Examiner William R. A. Jarvis

For: TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS — July 20, 2000

Assistant Commissioner for Patents
Washington, D.C. 20231

AMENDMENT

Sir:

This is in response to the first Office Action.

IN THE SPECIFICATION:

Please amend the first sentence of the specification as follows:

-- This is a continuation-in-part of Application Serial No. ~~09/256,388~~, filed on ~~February 24, 1999~~, now ~~abandoned, and~~ Application Serial No. ~~09/275,070~~, ~~now U.S. Patent No. 6,015,557~~. --

application 09/275,070 8/24/00
March 23, 1999 U.S. Patent 6,015,557, which is a continuation-in-part of
now abandoned 09/256,388, filed February 24, 1999,

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST-CLASS MAIL IN AN ENVELOPE ADDRESSED TO: ASSISTANT COMMISSIONER FOR PATENTS WASHINGTON, D.C. 20231 ON

DATE 7/20/00

BY

TNT INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

RELATED APPLICATION

This application is a continuation-in-part of application Ser. No. 09/275,070, filed on Mar. 23, 1999, now U.S. Pat. No. 6,015,557, which is a continuation-in-part of application Ser. No. 09/256,388, filed Feb. 24, 1999 now abandoned.

FIELD OF THE INVENTION

The present invention relates to tumor necrosis factor (TNF) antagonists or TNF blockers for the treatment of neurological disorders, trauma, injuries or compression; demyelinating neurological disorders, including multiple sclerosis; neurodegenerative diseases, including Alzheimer's disease; muscular disorders; and disorders of the optic nerve and retina (hereinafter "Neurologic and Related TNF Disorders"). More particularly, the TNF antagonists, TNF inhibitors or TNF blockers, are used for the treatment, prevention or amelioration of these "Neurologic and Related TNF Disorders" by modulating the action of TNF in the human body. The use of these TNF antagonists or TNF blockers results in the amelioration of these disorders and diseases and represents a novel use for this class of drugs.

BACKGROUND OF THE INVENTION

Neurological disorders due to demyelinating disease (e.g. multiple sclerosis), immune disease, inflammation, trauma, or compression, occur in different clinical forms depending upon the anatomic site and the cause and natural history of the physiological problem. For example, in Alzheimer's disease the brain undergoes a serious form of neurodegeneration of unknown etiology. Common to all of these disorders is the fact that they can cause permanent neurological damage, that damage can occur rapidly and be irreversible, and that current treatment of these conditions is unsatisfactory, often requiring surgery and/or the use of pharmacologic agents, which are often not completely successful.

These neurological conditions include acute spinal cord trauma, spinal cord compression, spinal cord hematoma, cord contusion (these cases are usually traumatic, such as motorcycle accidents or sports injuries); nerve compression, the most common condition being a herniated disc causing sciatic nerve compression, neuropathy, and pain; but also including cervical disc herniation, causing nerve compression in the neck; acute or chronic spinal cord compression from cancer (this is usually due to metastases to the spine, such as from prostate, breast or lung cancer); autoimmune disease of the nervous system; and demyelinating diseases, the most common condition being multiple sclerosis.

Steroid drugs such as cortisone that are used to treat many of the aforementioned neurological problems and conditions are particularly hazardous because they are used either at high dosage, with a corresponding increasing risk of side effects, or because they are used chronically, also increasing their adverse effects. Lastly, steroids are only partially effective or completely ineffective.

Tumor necrosis factor (TNF), a naturally occurring cytokine, plays a central role in the inflammatory response and in immune injury. TNF is formed by the cleavage of a precursor transmembrane protein, forming soluble molecules which aggregate to form trimolecular complexes. These complexes then bind to receptors found on a variety of cells. Binding produces an array of pro-inflammatory

effects, including release of other pro-inflammatory cytokines, including interleukin (IL)-6, IL-8, and IL-1; release of matrix metalloproteinases; and up regulation of the expression of endothelial adhesion molecules, further amplifying the inflammatory and immune cascade by attracting leukocytes into extravascular tissues. TNF is now well established as key in the pathogenesis of rheumatoid arthritis (RA) and Crohn's Disease.

Specific inhibitors of TNF, only recently commercially available, now provide the possibility of therapeutic intervention in TNF mediated diseases. Dramatic therapeutic success has already been demonstrated with infliximab, a chimeric anti-TNF monoclonal antibody (mAb), in treating Crohn's Disease and RA; and with etanercept, a recombinant fusion protein consisting of two soluble TNF receptors joined by the Fc fragment of a human IgG1 molecule, in treating RA and Psoriatic Arthritis. Other specific anti-TNF agents are under development, including D2E7 (a human anti-TNF mAb), CDP 571 (a chimeric, but 95% humanized, anti-TNF mAb), and a pegylated soluble TNF type 1 receptor. Additionally, thalidomide has been demonstrated to be a potent anti-TNF agent. Further, anti-TNF therapies may include gene therapy and the development of selective inhibitors of the TNF-alpha converting enzyme.

As with other organ systems, TNF has been shown to have a key role in the central nervous system. There is a need for TNF inhibitors that will open a new realm of therapeutic possibilities for a wide variety of neurological and related disorders. These disorders are diverse and include inflammatory and autoimmune disorders of the nervous system, including multiple sclerosis, Guillain Barre syndrome, and myasthenia gravis; degenerative disorders of the nervous system, including Alzheimer's disease, Parkinson's disease and Huntington's disease; disorders of related systems of the retina and of muscle, including optic neuritis, macular degeneration, diabetic retinopathy, dermatomyositis, amyotrophic lateral sclerosis, and muscular dystrophy; and injuries to the nervous system, including traumatic brain injury, acute spinal cord injury, and stroke.

The limited ability of the body to effect repair after injury to the nervous system, the devastating nature of these diseases and the lack of effective therapy all highlight the importance of early therapy aimed at preventing or limiting neuronal destruction. Anti-TNF therapies are ideally suited to this task because they have been demonstrated to dramatically limit inflammation by interrupting the inflammatory cascade at a fundamental level.

There remains a need for a new pharmacologic treatment of these aforementioned physiological problems of the nervous system associated with autoimmune disease, demyelinating diseases, neurodegenerative diseases, trauma, injuries and compression with the pharmacological use of TNF antagonists or TNF blockers, which are greatly beneficial for the large number of patients whom these conditions affect. Drugs which are powerful TNF blockers are etanercept, infliximab, pegylated soluble TNF Receptor Type I (PEGs TNF-R1), other agents containing soluble TNF receptors, CDP571 (a humanized monoclonal anti-TNF-alpha antibodies), thalidomide, phosphodiesterase 4 (IV) inhibitor thalidomide analogues and other phosphodiesterase IV inhibitors. Etanercept or infliximab may be used for the immediate, short term and long term (acute and chronic) blockade of TNF in order to minimize neurological damage mediated by TNF dependent processes occurring in the aforementioned neurological disorders. The use of these TNF antagonists or TNF blockers would result in the amelioration of these physiological neurological problems.

A

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ROBERT A. GREEN
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*MEMBER OF N.J. AND N.Y. BARS

PATENTS
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March 23, 1999

BY EXPRESS MAIL

Assistant Commissioner for Patents
Washington, D.C. 20231

File No.: TOBINICK 3.0-007 (CIP)
Inventor(s): Dr. Edward L. Tobinick
Title: TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

Assignee: None

Dear Sir:

Enclosed herewith are the following documents in the above-identified application for a Letters Patent of the United States:

1 Pages of Abstract
21 Pages of Specification
47 Number of Claims
none Sheets of Drawings
none Assignment for Recording
X Verified Statement for Small Entity Status
Declaration, Power of Attorney & Petition
Two (2) return-addressed postcards
(PLEASE PROVIDE FILING DATE & SERIAL NUMBER)
(attached to copy of this letter)
X PETITION TO MAKE SPECIAL; LIST OF PRIOR ART CITED BY APPLICANT; 3 PRIOR ART PATENTS; FEE ($130

Check No. 3002 in the amount of $753.00, calculated as follows:

Basic Fee (**Large Business $760.00) (*Small Business $380.00)	$380.00
Additional Fees:	
Total number of claims 47	
Total number of claims in excess of 20, 27 times (**$18)(*$9)	243.00
Number of independent claims 2	
Number of independent claims minus 3, --times (**$78)(*$39)	--
Assignment recording fee ($40)	--
Multiple dependent claims (**$260) (*$130)	--
TOTAL filing and assignment recording fees	$623.00
PETITION TO MAKE SPECIAL FEE	130.00
	~~$753.00~~

CONVENTION DATE _____ for _____ Appln. No. _____ is claimed.

Priority Document: ____Enclosed ____Will follow

Respectfully submitted,

EZRA SUTTON, Reg No. 25,770

ES/jmt
Enclosures

TOBINICK 3.0-007 (CIP)

TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

RELATED APPLICATION

This is a continuation-in-part of Application Serial No. 09/956,388, filed on February 24, 1999.

FIELD OF THE INVENTION

The present invention relates to tumor necrosis factor (TNF) antagonists or TNF blockers for the treatment of neurological disorders, trauma, injuries or compression; or demyelinating neurological disorders, including multiple sclerosis. More particularly, the TNF antagonists or TNF blockers, with or without the concurrent administration of methotrexate or Leflunomide, are used in a new treatment of these disorders by inhibiting the action of TNF in the cells of the human body. The use of these TNF antagonists or TNF blockers with methotrexate or Leflunomide results in the amelioration of these neurological conditions.

BACKGROUND OF THE INVENTION

Neurological disorders due to demyelinating disease (e.g. multiple sclerosis), immune disease, inflammation, trauma, or compression, occur in different clinical forms depending upon the anatomic site and the cause and natural history of the physiological problem. Common to all of these disorders is the fact that they can cause permanent neurological damage, that damage can occur rapidly and be irreversible, and that current treatment of these conditions is unsatisfactory, often requiring surgery

DECLARATION FOR PATENT APPLICATION

Docket No. TOBINICK 3.0-007(CIP)

As a below named inventor, I hereby [redacted] that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS, the specification of which

(check one) ☒ is attached hereto.

☐ was filed on _____ as Application Serial No. _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)
09/256,388	24 February 1999	pending
(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Ezra Sutton, Reg. No. 25,770

Address all telephone calls to _____ at telephone no. (732) 634-3520

Address all correspondence to EZRA SUTTON, P.A.
Plaza 9, 900 Route 9
Woodbridge, New Jersey 07095

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor Dr. Edward L. TOBINICK

Inventor's signature X _____ Date 3-20-99

Residence Los Angeles, California 90024-6903 Citizenship United States of America

Post Office Address 100 UCLA Medical Plaza, Suite 205
Los Angeles, California 90024-6903

Full name of second joint inventor, if any Arthur Jerome TOBINICK

Second Inventor's signature X _____ Date 3-20-99

Residence Los Angeles, California 90024-6903 Citizenship United States of America

Post Office Address 100 UCLA Medical Plaza, Suite 205
Los Angeles, California 90024-6903

(Supply similar information and signature for third and subsequent joint inventors.)

Applicant or Patentee: Dr. Edward L. TOBINICK
Arthur J. TOBINICK
Attorney's Docket No.: TOBINICK 3.0-007 (CIP)
Serial or Patent No.:
Filed or Issued:
Title: TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.2(f) AND 1.27(b) - INDEPENDENT INVENTOR

As a below-named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, Untied States Code, to the Patent and Trademark office with regard to the invention entitled TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS described in:

[X] the specification filed herewith
[ ] Application Serial No. _____, filed _____
[ ] Patent No. _____, issued _____.

I have not assigned, granted, conveyed, or licensed and am under no obligation, under contract or law to assign, grant, convey, or license, any rights in the invention to any person who could not be classified as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern, or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

[X] no such person, concern, or organization
[ ] persons, concerns, or organizations listed below*

*NOTE: Separate verified statements are required from each named person, concern, or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

FULL NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

FULL NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

FULL NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Dr. Edward L. TOBINICK	Arthur Jerome TOBINICK	
NAME OF INVENTOR	NAME OF INVENTOR	NAME OF INVENTOR
X Edward L. Tobinick	X Arthur J. Tobinick	
Signature of Inventor	Signature of Inventor	Signature of Inventor
3-20-99	3-20-99	
Date	Date	Date

TOBINICK 3.0-007 (CIP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of: DR. EDWARD L. TOBINICK, et al	:	
Serial No.	:	Group Art Unit
Filed:	:	Examiner
For: TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS	:	March 23, 1999

Assistant Commissioner for Patents
Washington, D.C 20231

PETITION TO MAKE SPECIAL
(MPEP Section 708.02)

Sir:

Applicant hereby files this Petition to make special this application for purposes of examination and payment of the issue fee, on the grounds of a pre-examination search. Applicant also submits the petition fee.

The application presents claims directed to a single invention. In case the Examiner believes that there is more than one invention, applicant hereby elects without traverse Claims 27 to 47.

SEARCH AREAS

A pre-examination search was made of the records of the U.S. Patent Office by applicant's attorney, Ezra Sutton. The field of search included Class 424, Subclasses 85.1, 133.1, 134.1, 143.1,

144.1, 145.1, and 158.1; Class 435, Subclasses 69.1, 69.7, 172.3, and 240.27; and Class 530, Subclasses 350, 351, 387.1, 387.3, 388.2, 388.23, 388.4, 866, and 868. Also, a computer search was performed using the terms TNF and tumor necrosis factor.

INVENTION SEARCHED

A method for inhibiting the action of TNF for treating neurological conditions in a human by administering a TNF antagonist for reducing damage to neuronal tissue or for modulating the immune response affecting neuronal tissue of the human. The TNF antagonist administered is selected from the group consisting of etanercept and infliximab. The TNF antagonist is administered subcutaneously, intravenously, intrathecally, or intramuscularly.

Methotrexate or Leflunomide may be administered concurrently with the TNF antagonist for demyelinating diseases and certain other neurological disorders.

PATENTS SELECTED IN SEARCH

U.S. Patent Nos.: 5,605,690

5,656,272

5,795,967

A copy of each patent is enclosed.

DISCUSSION OF PATENTS

U.S. Patent No. 5,605,690 discloses using TNF antagonists to suppress TNF-dependent inflammatory diseases, such as arthritis. However, this reference does not disclose treating the specific neurological disorders claimed in the present application.

U.S. Patent No. 5,656,272 discloses using TNF antagonists to treat Crohn's disease. However, this reference does not disclose treating the specific neurological disorders claimed in the present application.

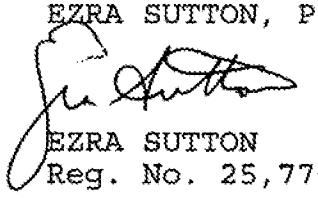
U.S. Patent No. 5,795,967 discloses using TNF antagonists to treat certain autoimmune diseases, such as arthritis, systemic lupus, and Crohn's disease. However, this reference does not disclose treating the specific neurological disorders claimed in the present application.

CONCLUSION

None of the prior art patents disclose or teach the specific subject matter recited in independent Claims 1 or 27, or render them obvious. Accordingly, this Petition should be granted.

Respectfully submitted,

EZRA SUTTON, P.A.



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ES/jmt

Enclosures

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO
09/275,070	03/23/1999	424	1614	TOBINICK-3.0

APPLICANT
EDWARD L TOBINICK, LOS ANGELES, CALIFORNIA; ARTHUR JEROME TOBINICK, LOS ANGELES, CALIFORNIA.

CONTINUING DOMESTIC DATA********
VERIFIED THIS APPLN IS A CIP OF 09/256,388 02/24/1999

371 (NAT'L STAGE) DATA********
VERIFIED

FOREIGN APPLICATIONS********
VERIFIED

FOREIGN FILING LICENSE GRANTED 05/07/1999 SMALL ENTITY

Foreign priority claimed O yes O no 35 USC 119 (a-d) conditions met O yes O no O Met after Allowance Verified and acknowledged _____ _____ Examiner's Name Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
	CA	0	47	2

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TITLE
TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
$**623	No. _____ to charge/credit DEPOSIT ACCOUNT NO. _____ for the following:	O All Fees O 1.16 Fees (Filing) O 1.17 Fees (Processing Ext. of Time) O 1.18 Fees (Issue) O Other _____ O Credit

TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

RELATED APPLICATION

This is a continuation-in-part of application Ser. No. 09/256,388, filed on Feb. 24, 1999, now abandoned.

FIELD OF THE INVENTION

The present invention relates to tumor necrosis factor (TNF) antagonists or TNF blockers for the treatment of neurological disorders, trauma, injuries or compression; or demyelinating neurological disorders, including multiple sclerosis. More particularly, the TNF antagonists or TNF blockers, with or without the concurrent administration of methotrexate or Leflunomide, are used in a new treatment of these disorders by inhibiting the action of TNF in the cells of the human body. The use of these TNF antagonists or TNF blockers with methotrexate or Leflunomide results in the amelioration of these neurological conditions.

BACKGROUND OF THE INVENTION

Neurological disorders due to demyelinating disease (e.g. multiple sclerosis), immune disease, inflammation, trauma, or compression, occur in different clinical forms depending upon the anatomic site and the cause and natural history of the physiological problem. Common to all of these disorders is the fact that they can cause permanent neurological damage, that damage can occur rapidly and be irreversible, and that current treatment of these conditions is unsatisfactory, often requiring surgery and/or the use of pharmacologic agents, which are often not completely successful.

These neurological conditions include acute spinal cord trauma, spinal cord compression, spinal cord hematoma, cord contusion (these cases are usually traumatic, such as motorcycle accidents or sports injuries); nerve compression, the most common condition being a herniated disc causing sciatic nerve compression, neuropathy, and pain; but also including cervical disc herniation, causing nerve compression in the neck; carpal tunnel syndrome (non-RA); acute or chronic spinal cord compression from cancer (this is usually due to metastases to the spine, such as from prostate, breast or lung cancer); autoimmune disease of the nervous system; and demyelinating diseases, the most common condition being multiple sclerosis.

Steroid drugs such as cortisone that are used to treat the aforementioned neurological problems and conditions are particularly hazardous because they are used either at high dosage, with a corresponding increasing risk of side effects, or because they are used chronically, also increasing their adverse effects. Lastly, steroids are only partially effective or completely ineffective.

There remains a need for a new pharmacologic treatment of these aforementioned physiological problems of the nervous system associated with autoimmune disease, demyelinating diseases, trauma, injuries and compression with the pharmacological use of TNF antagonists or TNF blockers, which are greatly beneficial for the large number of patients whom these conditions affect. Two new drugs which are powerful TNF blockers are etanercept and infliximab. Etanercept or infliximab may be used for the immediate, short term and long term (acute and chronic) blockade of TNF in order to minimize neurologic damage mediated by TNF dependent processes occurring in the aforementioned neurological disorders. The use of these TNF antagonists or TNF blockers would result in the amelioration of these physiological neurological problems. Concurrent administration of methotrexate or Leflunomide with either etanercept or infliximab is the preferred treatment for demyelinating diseases and certain other neurological disorders.

DESCRIPTION OF THE PRIOR ART

Pharmacologic chemical substances, compounds and agents which are used for the treatment of neurological disorders, trauma, injuries and compression having various organic structures and metabolic functions have been disclosed in the prior art. For example, U.S. Pat. Nos. 5,756,482 and 5,574,022 to ROBERTS et al disclose methods of attenuating physical damage to the nervous system and to the spinal cord after injury using steroid hormones or steroid precursors such as pregnenolone, and pregnenolone sulfate in conjunction with a non-steroidal anti-inflammatory substance such as indomethacin. These prior art patents do not teach the use of a TNF antagonist or TNF blocker for the suppression and inhibition of the action of TNF in the human body to treat neurological disease, trauma, injury or compression, or autoimmune neurologic disease as in the present invention.

U.S. Pat. No. 5,605,690 to JACOBS discloses a method for treating TNF-dependent inflammatory diseases such as arthritis by administering a TNF antagonist, such as soluble human TNFR (a sequence of amino acids), to a human. This prior art patent does not teach the use of a TNF antagonist or TNF blocker for the suppression and inhibition of the action of TNF in the human body to treat neurological disease, trauma, injury or compression, or demyelinating neurologic disease, as in the present invention.

U.S. Pat. No. 5,656,272 to LE et al discloses methods of treating TNF-alpha-mediated Crohn's disease using chimeric anti-TNF antibodies. This prior art patent does not teach the use of a TNF antagonist or TNF blocker for the suppression and inhibition of the action of TNF in the human body to treat neurological trauma, injury or compression, or autoimmune neurologic disease, as in the present invention.

U.S. Pat. No. 5,650,396 discloses a method of treating multiple sclerosis (MS) by blocking and inhibiting the action of TNF in a patient. This prior art patent does not teach the use of the TNF antagonist as in the present invention.

None of the prior art patents disclose or teach the use of the TNF antagonist or TNF blocker of the present invention with the concurrent administration of methotrexate or Leflunomide for suppression and inhibition of the action of TNF in a human to treat neurological disease, trauma, injury or compression, or demyelinating neurologic disease, in which the TNF antagonist gives the patient a better opportunity to heal, slows disease progression, prevents neurological damage, or otherwise improves the patient's health.

Accordingly, it is an object of the present invention to provide a TNF antagonist, with or without the concurrent administration of methotrexate or Leflunomide, for a new pharmacologic treatment of neurological disorders, trauma, injuries and compression affecting the nervous system of the human body, or demyelinating neurologic disease, such that the use of these TNF antagonists will result in the amelioration of these neurological conditions.

Another object of the present invention is to provide a TNF antagonist, with or without the concurrent administration of methotrexate or Leflunomide, for providing suppression and inhibition of the action of TNF in a human to treat neurological injury, trauma or compression, or demyelinating neurologic disease.

DECLARATION FOR PATENT APPLICATION

Docket No. TOBINICK 3.0-007

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS, the specification of which

(check one) ☒ is attached hereto.

☐ was filed on _____ as Application Serial No. _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Ezra Sutton, Reg. No. 25,770

Address all telephone calls to _____ at telephone no. (732) 634-3520

Address all correspondence to EZRA SUTTON, P.A.
Plaza 9, 900 Route 9
Woodbridge, New Jersey 07095

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor Dr. Edward L. TOBINICK

Inventor's signature X _____ Date X FEBRUARY 21, 1999

Residence Los Angeles, California 90024-6903 Citizenship United States of America

Post Office Address 100 UCLA Medical Plaza, Suite 205
Los Angeles, California 90024-6903

Full name of second joint inventor, if any ARTHUR JEROME TOBINICK

Second Inventor's signature _____ Date February 21, 1999

Residence LOS ANGELES, CALIFORNIA 90024-6903 Citizenship USA

Post Office Address 100 UCLA MEDICAL PLAZA, SUITE 205
LOS ANGELES, CALIFORNIA 90024-6903

(Supply similar information and signature for third and subsequent joint inventors.)

Applicant or Patentee: Dr. Edward L. TOBINICK / Arthur J. Tobinick
Serial or Patent No.: _____
Filed or Issued: _____
Attorney's Docket No.: TOBINICK 3.0-007
Title: TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.2(f) AND 1.27(b) - INDEPENDENT INVENTOR

As a below-named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, Untied States Code, to the Patent and Trademark office with regard to the invention entitled TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS described in:

[X] the specification filed herewith
[ ] Application Serial No. _____, filed _____
[ ] Patent No. _____, issued _____.

I have not assigned, granted, conveyed, or licensed and am under no obligation, under contract or law to assign, grant, convey, or license, any rights in the invention to any person who could not be classified as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern, or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

[X] no such person, concern, or organization
[ ] persons, concerns, or organizations listed below*

*NOTE: Separate verified statements are required from each named person, concern, or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

FULL NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

FULL NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

FULL NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Dr. Edward L. TOBINICK	ARTHUR JEROME TOBINICK	
NAME OF INVENTOR	NAME OF INVENTOR	NAME OF INVENTOR
X _____	_____	_____
Signature of Inventor	Signature of Inventor	Signature of Inventor
X Feb. 21, 1999	Feb 21, 1999	
Date	Date	Date

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
09/256,388	02/24/99	514	1614	3.0-007

APPLICANT

EDWARD L. TOBINICK, LOS ANGELES, CA.

CONTINUING DOMESTIC DATA********
VERIFIED

_____

371 (NAT'L STAGE) DATA********
VERIFIED

_____

FOREIGN APPLICATIONS********
VERIFIED

_____

IF REQUIRED, FOREIGN FILING LICENSE GRANTED 03/15/99 ** SMALL ENTITY **

Foreign Priority claimed 35 USC 119 (a-d) conditions met	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐yes ☐no ☐yes ☐no ☐Met after Allowance Verified and Acknowledged _____ Examiner's Initials _____ Initials	CA	0	24	1

ADDRESS

EZRA SUTTON
PLAZA 9 ROUTE 9
WOODBRIDGE NJ 07095

TITLE

TUMOR NECROSIS FACTORS ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

FILING FEE RECEIVED		
$416	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT NO. _____ for the following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

DECLARATION FOR PATENT APPLICATION

Docket No. TOBINICK 3.0-007

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS, the specification of which

(check one) ☒ is attached hereto.

☐ was filed on _____ as Application Serial No. _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Ezra Sutton, Reg. No. 25,770

Address all telephone calls to _____ at telephone no. (732) 634-3520.

Address all correspondence to EZRA SUTTON, P.A.
Plaza 9, 900 Route 9
Woodbridge, New Jersey 07095

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor Dr. Edward L. TOBINICK

Inventor's signature X _____ Date X February 21, 1999

Residence Los Angeles, California 90024-6903 Citizenship United States of America

Post Office Address 100 UCLA Medical Plaza, Suite 205
Los Angeles, California 90024-6903

Full name of second joint inventor, if any ARTHUR JEROME TOBINICK

Second Inventor's signature _____ Date February 21, 1999

Residence Los Angeles, California 90024-6903 Citizenship USA

Post Office Address 100 UCLA Medical Plaza, Suite 205
Los Angeles, California 90024-6903

(Supply similar information and signature for third and subsequent joint inventors.)

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EZRA SUTTON*
OF COUNSEL
ROBERT A. GREEN
DAVID L. DAVIS

*MEMBER OF N.J. AND N.Y. BARS

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FAX: (732) 634-3511

February 24, 1999

BY EXPRESS MAIL

Assistant Commissioner for Patents
Washington, D.C. 20231

File No.: TOBINICK 3.0-007
Inventor(s): Dr. Edward L. Tobinick
Title: TUMOR NECROSIS FACTORS ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

Assignee: None

Dear Sir:

Enclosed herewith are the following documents in the above-identified application for a Letters Patent of the United States:

1 Pages of Abstract
16 Pages of Specification
24 Number of Claims
-- Sheets of Drawings
-- Assignment for Recording

x Verified Statement for Small Entity Status
Declaration, Power of Attorney & Petition
Two (2) return-addressed postcards
(PLEASE PROVIDE FILING DATE & SERIAL NUMBER)
(attached to copy of this letter)

Check No. _____ in the amount of $416.00, calculated as follows:

Basic Fee (**Large Business $760.00) (*Small Business $380.00)	$380.00
Additional Fees:	
Total number of claims 24	
Total number of claims in excess of 20, 4 times (**$18)(*$9)	36.00
Number of independent claims 1	
Number of independent claims minus 3, -- times (**$78)(*$39)	--
Assignment recording fee ($40)	--
Multiple dependent claims (**$260) (*$130)	--
TOTAL filing and assignment recording fees	$416.00

CONVENTION DATE _____ for _____ Appln. No. _____ is claimed.

Priority Document: ____Enclosed ____Will follow

Respectfully submitted,

EZRA SUTTON, Reg No. 25,770

ES/jmt
Enclosures

TUMOR NECROSIS FACTOR ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

FIELD OF THE INVENTION

The present invention relates to tumor necrosis factor (TNF) antagonists or TNF blockers for the treatment of neurological disorders, trauma, injuries or compression; or autoimmune neurological disorders. More particularly, the TNF antagonists or TNF blockers are used in a new treatment of these disorders by inhibiting the action of TNF in the cells of the human body. The use of these TNF antagonists or TNF blockers results in the amelioration of these neurological conditions.

BACKGROUND OF THE INVENTION

Neurological disorders due to demyelinating disease, immune disease, inflammation, trauma, or compression, occur in different clinical forms depending upon the anatomic site and the cause and natural history of the physiological problem. Common to all of these disorders is the fact that they can cause permanent neurological damage, that damage can occur rapidly and be irreversible, and that current treatment of these conditions is unsatisfactory, often requiring surgery and/or the use of pharmacologic agents, which are often not completely successful.

These neurological conditions include acute spinal cord trauma, spinal cord compression, spinal cord hematoma, cord contusion (these cases are usually traumatic, such as motorcycle accidents or sports injuries); nerve compression, the most common condition being a herniated disc causing sciatic nerve compression,

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/256,388	02/24/99	TOBINICK E	3.0-007

HM12/0927

EZRA SUTTON
PLAZA 9 ROUTE 9
WOODBRIDGE NJ 07095

EXAMINER	
JARVIS,W	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 09/27/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Notice of Abandonment

Application No.	Applic[illegible]
09/256,388	Tobinick
Examiner	Group Art Unit
William R. A. Jarvis	1614

This application is abandoned in view of:

☐ applicant's failure to timely file a proper response to the Office letter mailed on _____ .

☐ A response (with a Certificate of Mailing or Transmission of _____) was received on _____, which is after the expiration of the period for response (including a total extension of time of ____ month(s)) which expired on _____ .

☐ A proposed response was received on _____, but it does not constitute a proper response to the final rejection.

(A proper response to a final rejection consists only of: a timely filed amendment which places the application in condition for allowance; a Notice of Appeal; or the filing of a continuing application under 37 CFR 1.62 (FWC)).

☐ No response has been received.

☐ applicant's failure to timely pay the required issue fee within the statutory period of three months from the mailing date of the Notice of Allowance.

☐ The issue fee (with a Certificate of Mailing or Transmission of _____) was received on _____ .

☐ The submitted issue fee of $_____ is insufficient. The issue fee required by 37 CFR 1.18 is $_____ .

☐ The issue fee has not been received.

☐ applicant's failure to timely file new formal drawings as required in the Notice of Allowability.

☐ Proposed new formal drawings (with a Certificate of Mailing or Transmission of _____) were received on _____ .

☐ The proposed new formal drawings filed _____ are not acceptable.

☐ No proposed new formal drawings have been received.

☐ the express abandonment under 37 CFR 1.62(g) in favor of the FWC application filed on _____ .

☒ the letter of express abandonment which is signed by the attorney or agent of record, the assignee of the entire interest, or all of the applicants.

☐ the letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34(a)) upon the filing of a continuing application.

☐ the decision by the Board of Patent Appeals and Interferences rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

☐ the reason(s) below:

William Jarvis

WILLIAM R. A. JARVIS
PRIMARY EXAMINER
ART UNIT 1614

OFFICIAL
ad. Journ
9/16/99

#2
JRP
9/24/99

LAW OFFICES
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EZRA SUTTON*
OF COUNSEL
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*MEMBER OF N.J. AND N.Y. BARS

Date 9/16/99

TO: EXR. WILLIAM JARVIS

FAX NO. 703-308-7924

FROM: EZRA SUTTON

FAX NO. 1-732-634-3511
PHONE: 1-732-634-3520

TOTAL NUMBER OF PAGES: 1

Re: S.N. 09/256,388

Applicant hereby abandons the above-identified application in favor of Appln. S.N. 09/275,070, which has been allowed by Examiner Jarvis.

Ezra Sutton
REG. NO. 25,170

agreeing to the change of inventorship in the patent; such statement must comply with the requirements of 37 CFR 3.73(b); and (4) the fee set forth in 37 CFR 1.20(b). This petition lacks item(s) [7].

---

[8]
Supervisory Patent Examiner,
Art Unit [9],
Technology Center [10]
[11]

Examiner Note:

1. If each of the four specified items has been submitted but one or more is insufficient, the petition should be denied. See paragraph 10.17. However, if the above noted deficiency can be cured by the submission of a renewed petition, a dismissal would be appropriate.
2. If the petition includes a request for suspension of the rules (37 CFR 1.183) of one or more provisions of 37 CFR 1.324 that are required by the statute (35 U.S.C. 256), form paragraph 10.18 should follow this form paragraph.
3. In bracket 7, pluralize as necessary and insert the item number(s) which are missing.
4. In bracket 11, insert correspondence address of record.
5. This form paragraph is printed with the USPTO letterhead.

¶ *10.17 Petition Under 37 CFR 1.324, Denied*

In re Patent No. [1]	:
Issue Date: [2]	:**DECISION DENYING PETITION**
Appl. No.: [3]	:*37 CFR 1.324*
Filed: [4]	:
For: [5]	:

This is a decision on the petition filed [6] to correct inventorship under 37 CFR 1.324.

The petition is denied.

[7]

---

[8]
Supervisory Patent Examiner,
Art Unit [9],
Technology Center [10]
[11]

Examiner Note:

1. In bracket 7, a full explanation of the deficiency must be provided.
2. If the petition lacks one or more of the required parts set forth in 37 CFR 1.324, it should be dismissed using form paragraph 10.14 or 10.20, rather than being denied.
3. In bracket 11, insert correspondence address of record.
4. This form paragraph is printed with the USPTO letterhead.

¶ *10.18 Waiver of Requirements of 37 CFR 1.324 Under 37 CFR 1.183, Dismissed*

Suspension of the rules under 37 CFR 1.183 may be granted for any requirement of the regulations which is not a requirement of the statutes. In this instance, 35 U.S.C. 256 requires [1]. Accordingly, the petition under 37 CFR 1.183 is dismissed as moot.

Examiner Note:

1. This form paragraph should follow form paragraph 10.16 whenever the petition requests waiver of one or more of the provisions of 37 CFR 1.324 that are also requirements of 35 U.S.C. 256.
2. If the petition requests waiver of requirements of 37 CFR 1.324 that are not specific requirements of the statute (i.e., the fee or the oath or declaration by all inventors), the application must be forwarded to a petitions attorney in the Office of the Deputy Commissioner for Patent Examination Policy for decision.

1481.03 Correction of 35 U.S.C. 119 and 35 U.S.C. 120 Benefits [R-7]

I. CORRECTION TO PERFECT CLAIM FOR 35 U.S.C. 119 (a)-(d) AND (f) BENEFITS

See MPEP § 201.16 for a discussion of when 35 U.S.C. 119 (a)-(d) and (f) benefits can be perfected by certificate of correction.

II. CORRECTION AS TO 35 U.S.C. 120 AND 35 U.S.C. 119(e) BENEFITS

*A. For Applications Filed **>Before< November 29, 2000*

For applications filed **>before< November 29, 2000, it is the version of 37 CFR 1.78, which was in effect as of November 29, 2000, that applies. The pre-November 29, 2000 version reads as follows:

37 CFR 1.78. Claiming benefit of earlier filing date and cross-references to other applications.

(a)(1) A nonprovisional application may claim an invention disclosed in one or more prior filed copending nonprovisional applications or copending international applications designating the United States of America. In order for a nonprovisional application to claim the benefit of a prior filed copending nonprovisional application or copending international application designating the United States of America, each prior application must name as an inventor at least one inventor named in the later filed nonprovisional application and disclose the named inventor's invention claimed in at least one claim of the later filed nonprovisional application in the manner provided by the first paragraph of 35 U.S.C. 112. In addition, each prior application must be:

(i) An international application entitled to a filing date in accordance with PCT Article 11 and designating the United States of America; or

(ii) Complete as set forth in § 1.51(b); or

(iii) Entitled to a filing date as set forth in § 1.53(b) or § 1.53(d) and include the basic filing fee set forth in § 1.16; or

(iv) Entitled to a filing date as set forth in § 1.53(b) and have paid therein the processing and retention fee set forth in § 1.21(l) within the time period set forth in § 1.53(f).

(2) Except for a continued prosecution application filed under § 1.53(d), any nonprovisional application claiming the benefit of one or more prior filed copending nonprovisional applications or international applications designating the United States of America must contain a reference to each such prior application, identifying it by application number (consisting of the series code and serial number) or international application number and international filing date and indicating the relationship of the applications. Unless the reference required by this paragraph is included in an application data sheet (§ 1.76), the specification must contain or be amended to contain such reference in the first sentence following any title. The request for a continued prosecution application under § 1.53(d) is the specific reference required by 35 U.S.C. 120 to the prior application. The identification of an application by application number under this section is the specific reference required by 35 U.S.C. 120 to every application assigned that application number. Cross-references to other related applications may be made when appropriate (see § 1.14(a)).

(3) A nonprovisional application other than for a design patent may claim an invention disclosed in one or more prior filed copending provisional applications. In order for a nonprovisional application to claim the benefit of one or more prior filed copending provisional applications, each prior provisional application must name as an inventor at least one inventor named in the later filed nonprovisional application and disclose the named inventor's invention claimed in at least one claim of the later filed nonprovisional application in the manner provided by the first paragraph of 35 U.S.C. 112. In addition, each prior provisional application must be entitled to a filing date as set forth in § 1.53(c), have any required English-language translation filed therein within the time period set forth in § 1.52(d), and have paid therein the basic filing fee set forth in § 1.16(k) within the time period set forth in § 1.53(g).

(4) Any nonprovisional application claiming the benefit of one or more prior filed copending provisional applications must contain a reference to each such prior provisional application, identifying it as a provisional application, and including the provisional application number (consisting of series code and serial number). Unless the reference required by this paragraph is included in an application data sheet (§ 1.76), the specification must contain or be amended to contain such reference in the first sentence following any title.

*****

Under certain conditions specified below, a Certificate of Correction can be used, with respect to 35 U.S.C. 120 and 119(e) priority, to correct:

(A) the failure to make reference to a prior copending application pursuant to 37 CFR 1.78(a)(2) and (a)(4); or

(B) an incorrect reference to a prior copending application pursuant to 37 CFR 1.78(a)(2) and (a)(4).

For all situations other than where priority is based upon 35 U.S.C. 365(c), the conditions are as follows:

(A) for 35 U.S.C. 120 priority, all requirements set forth in 37 CFR 1.78(a)(1) must have been met in the application which became the patent to be corrected;

(B) for 35 U.S.C. 119(e) priority, all requirements set forth in 37 CFR 1.78(a)(3) must have been met in the application which became the patent to be corrected; and

(C) it must be clear from the record of the patent and the parent application(s) that priority is appropriate. See MPEP § 201.11 for requirements under 35 U.S.C. 119(e) and 120.

Where 35 U.S.C. 120 and 365(c) priority based on an international application is to be asserted or corrected in a patent via a Certificate of Correction, the following conditions must be satisfied:

(A) all requirements set forth in 37 CFR 1.78(a)(1) must have been met in the application which became the patent to be corrected;

(B) it must be clear from the record of the patent and the parent application(s) that priority is appropriate (see MPEP § 201.11); and

(C) the patentee must submit with the request for the certificate copies of documentation showing designation of states and any other information needed to make it clear from the record that the 35 U.S.C. 120 priority is appropriate. See MPEP § 201.13(b) as to the requirements for 35 U.S.C. 120 priority based on an international application.

If all the above-stated conditions are satisfied, a Certificate of Correction can be used to amend the patent to make reference to a prior copending application, or to correct an incorrect reference to the prior copending application. Note *In re Schuurs*, 218 USPQ 443 (Comm'r Pat. 1983) which suggests that a Certificate of Correction is an appropriate remedy for correcting, in a patent, reference to a prior copending application. Also, note *In re Lambrech*, 202 USPQ

620 (Comm'r Pat. 1976), citing *In re Van Esdonk*, 187 USPQ 671 (Comm'r Pat. 1975).

If any of the above-stated conditions is not satisfied, the filing of a reissue application (see MPEP § 1401 - § 1460) would be appropriate to pursue the desired correction of the patent.

B. For Applications Filed on or After November 29, 2000

For applications filed on or after November 29, 2000, the version of 37 CFR 1.78 reproduced below applies (note that amendments to 37 CFR 1.78 took effect on November 29, 2000, December 28, 2001, May 1, 2003, January 21, 2004, September 21, 2004, December 8, 2004, * July 1, 2005>, and November 25, 2005<).

37 CFR 1.78. Claiming benefit of earlier filing date and cross-references to other applications.

(a)(1) A nonprovisional application or international application designating the United States of America may claim an invention disclosed in one or more prior-filed copending nonprovisional applications or international applications designating the United States of America. In order for an application to claim the benefit of a prior-filed copending nonprovisional application or international application designating the United States of America, each prior-filed application must name as an inventor at least one inventor named in the later-filed application and disclose the named inventor's invention claimed in at least one claim of the later-filed application in the manner provided by the first paragraph of 35 U.S.C. 112. In addition, each prior-filed application must be:

(i) An international application entitled to a filing date in accordance with PCT Article 11 and designating the United States of America; or

(ii) Entitled to a filing date as set forth in § 1.53(b) or § 1.53(d) and have paid therein the basic filing fee set forth in § 1.16 within the pendency of the application.

(2)(i) Except for a continued prosecution application filed under § 1.53(d), any nonprovisional application or international application designating the United States of America claiming the benefit of one or more prior-filed copending nonprovisional applications or international applications designating the United States of America must contain or be amended to contain a reference to each such prior-filed application, identifying it by application number (consisting of the series code and serial number) or international application number and international filing date and indicating the relationship of the applications. Cross references to other related applications may be made when appropriate (see § 1.14).

(ii) This reference must be submitted during the pendency of the later-filed application. If the later-filed application is an application filed under 35 U.S.C. 111(a), this reference must also be submitted within the later of four months from the actual filing date of the later-filed application or sixteen months from the filing date of the prior-filed application. If the later-filed application is a nonprovisional application which entered the national stage from an international application after compliance with 35 U.S.C. 371, this reference must also be submitted within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371 (b) or (f) in the later-filed international application or sixteen months from the filing date of the prior-filed application. These time periods are not extendable. Except as provided in paragraph (a)(3) of this section, the failure to timely submit the reference required by 35 U.S.C. 120 and paragraph (a)(2)(i) of this section is considered a waiver of any benefit under 35 U.S.C. 120, 121, or 365(c) to such prior-filed application. The time periods in this paragraph do not apply if the later-filed application is:

(A) An application for a design patent;

(B) An application filed under 35 U.S.C. 111 (a) before November 29, 2000; or

(C) A nonprovisional application which entered the national stage after compliance with 35 U.S.C. 371 from an international application filed under 35 U.S.C. 363 before November 29, 2000.

(iii) If the later-filed application is a nonprovisional application, the reference required by this paragraph must be included in an application data sheet (§ 1.76), or the specification must contain or be amended to contain such reference in the first sentence(s) following the title.

(iv) The request for a continued prosecution application under § 1.53(d) is the specific reference required by 35 U.S.C. 120 to the prior-filed application. The identification of an application by application number under this section is the identification of every application assigned that application number necessary for a specific reference required by 35 U.S.C. 120 to every such application assigned that application number.

(3) If the reference required by 35 U.S.C. 120 and paragraph (a)(2) of this section is presented after the time period provided by paragraph (a)(2)(ii) of this section, the claim under 35 U.S.C. 120, 121, or 365(c) for the benefit of a prior-filed copending nonprovisional application or international application designating the United States of America may be accepted if the reference identifying the prior-filed application by application number or international application number and international filing date was unintentionally delayed. A petition to accept an unintentionally delayed claim under 35 U.S.C. 120, 121, or 365(c) for the benefit of a prior-filed application must be accompanied by:

(i) The reference required by 35 U.S.C. 120 and paragraph (a)(2) of this section to the prior-filed application, unless previously submitted;

(ii) The surcharge set forth in § 1.17(t); and

(iii) A statement that the entire delay between the date the claim was due under paragraph (a)(2)(ii) of this section and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional.

(4) A nonprovisional application, other than for a design patent, or an international application designating the United States of America may claim an invention disclosed in one or

more prior-filed provisional applications. In order for an application to claim the benefit of one or more prior-filed provisional applications, each prior-filed provisional application must name as an inventor at least one inventor named in the later-filed application and disclose the named inventor's invention claimed in at least one claim of the later-filed application in the manner provided by the first paragraph of 35 U.S.C. 112. In addition, each prior-filed provisional application must be entitled to a filing date as set forth in § 1.53(c), and the basic filing fee set forth in § 1.16(d) must be paid within the time period set forth in § 1.53(g).

(5)(i) Any nonprovisional application or international application designating the United States of America claiming the benefit of one or more prior-filed provisional applications must contain or be amended to contain a reference to each such prior-filed provisional application, identifying it by the provisional application number (consisting of series code and serial number).

(ii) This reference must be submitted during the pendency of the later-filed application. If the later-filed application is an application filed under 35 U.S.C. 111(a), this reference must also be submitted within the later of four months from the actual filing date of the later-filed application or sixteen months from the filing date of the prior-filed provisional application. If the later-filed application is a nonprovisional application which entered the national stage from an international application after compliance with 35 U.S.C. 371, this reference must also be submitted within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) in the later-filed international application or sixteen months from the filing date of the prior-filed provisional application. These time periods are not extendable. Except as provided in paragraph(a)(6) of this section, the failure to timely submit the reference is considered a waiver of any benefit under 35 U.S.C. 119(e) to such prior-filed provisional application. The time periods in this paragraph do not apply if the later-filed application is:

(A) An application filed under 35 U.S.C. 111(a) before November 29, 2000; or

(B) A nonprovisional application which entered the national stage after compliance with 35 U.S.C. 371 from an international application filed under 35 U.S.C. 363 before November 29, 2000.

(iii) If the later-filed application is a nonprovisional application, the reference required by this paragraph must be included in an application data sheet (§ 1.76), or the specification must contain or be amended to contain such reference in the first sentence(s) following the title.

(iv) If the prior-filed provisional application was filed in a language other than English and both an English-language translation of the prior-filed provisional application and a statement that the translation is accurate were not previously filed in the prior-filed provisional application, applicant will be notified and given a period of time within which to file, in the prior-filed provisional application, the translation and the statement. If the notice is mailed in a pending nonprovisional application, a timely reply to such a notice must include the filing in the nonprovisional application of either a confirmation that the translation and statement were filed in the provisional application, or an amendment or Supplemental Application Data Sheet withdrawing the benefit claim, or the nonprovisional application will be abandoned. The translation and statement may be filed in the provisional application, even if the provisional application has become abandoned.

(6) If the reference required by 35 U.S.C. 119(e) and paragraph (a)(5) of this section is presented in a nonprovisional application after the time period provided by paragraph (a)(5)(ii) of this section, the claim under 35 U.S.C. 119(e) for the benefit of a prior filed provisional application may be accepted during the pendency of the later-filed application if the reference identifying the prior-filed application by provisional application number was unintentionally delayed. A petition to accept an unintentionally delayed claim under 35 U.S.C. 119(e) for the benefit of a prior filed provisional application must be accompanied by:

(i) The reference required by 35 U.S.C. 119(e) and paragraph (a)(5) of this section to the prior-filed provisional application, unless previously submitted;

(ii) The surcharge set forth in § 1.17(t); and

(iii) A statement that the entire delay between the date the claim was due under paragraph (a)(5)(ii) of this section and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional.

(b) Where two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application.

(c) If an application or a patent under reexamination and at least one other application naming different inventors are owned by the same person and contain conflicting claims, and there is no statement of record indicating that the claimed inventions were commonly owned or subject to an obligation of assignment to the same person at the time the later invention was made, the Office may require the assignee to state whether the claimed inventions were commonly owned or subject to an obligation of assignment to the same person at the time the later invention was made, and if not, indicate which named inventor is the prior inventor. Even if the claimed inventions were commonly owned, or subject to an obligation of assignment to the same person, at the time the later invention was made, the conflicting claims may be rejected under the doctrine of double patenting in view of such commonly owned or assigned applications or patents under reexamination.

Under no circumstances can a Certificate of Correction be employed to correct an applicant's mistake by adding or correcting a priority claim under 35 U.S.C. 119(e) for an application filed on or after November 29, 2000.

Section 4503 of the American Inventors Protection Act of 1999 (AIPA) amended 35 U.S.C. 119(e)(1) to state that:

> No application shall be entitled to the benefit of an earlier filed provisional application under this subsection unless an amendment containing the specific reference to the earlier filed provisional application is submitted at such

> time during the pendency of the application as required by the Director. The Director may consider the failure to submit such an amendment within that time period as a waiver of any benefit under this subsection. The Director may establish procedures, including the payment of a surcharge, to accept an unintentionally delayed submission of an amendment under this section ***during the pendency of the application***. (emphasis added)

A Certificate of Correction is NOT a valid mechanism for adding or correcting a priority claim under 35 U.S.C. 119(e) after a patent has been granted on an application filed on or after November 29, 2000.

Under certain conditions as specified below, however, a Certificate of Correction can still be used, with respect to 35 U.S.C. 120 priority, to correct:

(A) the failure to make reference to a prior copending application pursuant to 37 CFR 1.78(a)(2); or

(B) an incorrect reference to a prior copending application pursuant to 37 CFR 1.78(a)(2).

Where priority is based upon 35 U.S.C. 120 to **a national application**, the following conditions must be satisfied:

(A) all requirements set forth in 37 CFR 1.78(a)(1) must have been met in the application which became the patent to be corrected;

(B) it must be clear from the record of the patent and the parent application(s) that priority is appropriate (see MPEP § 201.11); and

(C) a grantable petition to accept an unintentionally delayed claim for the benefit of a prior application must be filed, including a surcharge as set forth in 37 CFR 1.17(t), as required by 37 CFR 1.78(a)(3).

Where 35 U.S.C. 120 and 365(c) priority based on **an international application** is to be asserted or corrected in a patent via a Certificate of Correction, the following conditions must be satisfied:

(A) all requirements set forth in 37 CFR 1.78(a)(1) must have been met in the application which became the patent to be corrected;

(B) it must be clear from the record of the patent and the parent application(s) that priority is appropriate (see MPEP § 201.11);

(C) the patentee must submit together with the request for the certificate, copies of documentation showing designation of states and any other information needed to make it clear from the record that the 35 U.S.C. 120 priority is appropriate (see MPEP § 201.13(b) as to the requirements for 35 U.S.C. 120 priority based on an international application; and

(D) a grantable petition to accept an unintentionally delayed claim for the benefit of a prior application must be filed, including a surcharge as set forth in 37 CFR 1.17(t), as required by 37 CFR 1.78(a)(3).

If all the above-stated conditions are satisfied, a Certificate of Correction can be used to amend the patent to make reference to a prior copending application, or to correct an incorrect reference to the prior copending application, for benefit claims under 35 U.S.C. 120 and 365(c).

If any of the above-stated conditions is not satisfied, the filing of a reissue application (see MPEP § 1401 - § 1460) may be appropriate to pursue the desired correction of the patent for benefit claims under 35 U.S.C. 120 and 365(c).

1485 Handling of Request for Certificates of Correction [R-7]

A request for a Certificate of Correction should be addressed to:

Commissioner for Patents
Office of Patent Publication
ATTN: Certificate of Correction Branch
P.O. Box 1450
Alexandria, VA 22313-1450

Requests for Certificates of Correction will be forwarded to the Certificate of Correction Branch of the Office of Patent Publication, where they will be listed in a permanent record book.

If the patent is involved in an interference, a Certificate of Correction under 37 CFR 1.324 will not be issued unless a corresponding motion under 37 CFR 41.121(a)(2) or 41.121(a)(3) has been granted by the administrative patent judge. Otherwise, determination as to whether an error has been made, the responsibility for the error, if any, and whether the error is of such a nature as to justify the issuance of a Certificate of Correction will be made by the Certificate of Correction Branch. If a report is necessary in making such determination, the case will be forwarded to the appropriate group with a request that the report be furnished. If no certificate is to issue, the party making

04-06-01

Exhibit 17

A

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A PROFESSIONAL CORPORATION

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April 5, 2001
BY EXPRESS MAIL

Assistant Commissioner for Patents
Washington, D.C. 20231

File No.: TOBINICK 3.0-013
Inventor(s): Edward L. Tobinick, M.D.
Title: CYTOKINE ANTAGONISTS FOR THE TREATMENT OF LOCALIZED DISORDERS
Assignee: None

Dear Sir:

Enclosed herewith are the following documents in the above-identified application for a Letters Patent of the United States:

1 Pages of Abstract
25 Pages of Specification
39 Number of Claims
-- Sheets of Drawings
--- Assignment for Recording
X Verified Statement for Small Entity Status
Declaration, Power of Attorney & Petition
Two (2) return-addressed postcards
(PLEASE PROVIDE FILING DATE & SERIAL NUMBER)
(attached to copy of this letter)
x **Petition to Make Special; List of Prior Art; 6 prior art documents**

Check No. 5338 in the amount of $1,096, calculated as follows:

Basic Fee (**Large Business $710.00) (*Small Business $355.00)	$355
Additional Fees:	
Total number of claims 39	
Total number of claims in excess of 20, 19 times (**$18)(*$9)	171
Number of independent claims 14	
Number of independent claims minus 3, 11 times (**$80)(*$40)	440
Assignment recording fee ($40)	
Multiple dependent claims (**$270) (*$135)	
Petition to Make Special Fee	130
TOTAL filing and assignment recording fees	$1,096

CONVENTION DATE None for _____ Appln. No. _____
is claimed. Priority Document: ___ Enclosed ___ Will follow

Respectfully submitted,

EZRA SUTTON, Reg No. 25,770

ES/jmt
Enclosures

TOBINICK 3.0-013

CYTOKINE ANTAGONISTS FOR THE TREATMENT OF LOCALIZED DISORDERS

RELATED APPLICATIONS

This is a continuation-in-part of Application Serial No. 09/563,651, filed on May 2, 2000, which is a continuation-in-part of Application Serial No. 09/476,643, filed on December 31, 1999, now U.S. Patent No. 6,177,077, which is a continuation-in-part of Application Serial No. 09/275,070, filed on March 23, 1999, now U.S. Patent No. 6,015,557, which is a continuation-in-part of Application Serial No. 09/256,388, filed on February 24, 1999, now abandoned.

FIELD OF THE INVENTION

The present invention relates to specific cytokine antagonists which are provided for the treatment and prevention of damage to the optic nerve, other cranial nerves, brain, spinal cord, nerve roots, peripheral nerves or muscles caused by any one of the following: a herniated nucleus pulposus, osteoarthritis, other forms of arthritis, disorders of bone, disease, or trauma. More particularly, the cytokine antagonists are used in a new treatment of these disorders utilizing localized anatomic administration which causes inhibition of the action of the corresponding pro-inflammatory cytokine in a localized anatomic area of the human body. The administration of these cytokine antagonists is performed by anatomically localized administration which includes, but is not limited to the following routes: perilesional; intralesional; and transconjunctival (for disorders of the optic nerve). Perilesional routes as mentioned above include, but are not limited to, subcutaneous, intramuscular, and epidural routes of administration.

Exhibit 18

DECLARATION FOR PATENT APPLICATION

Docket No. TOBINICK 3.0-013

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled CYTOKINE ANTAGONISTS FOR THE TREATMENT OF LOCALIZED DISORDERS, the specification of which

(check one) [X] is attached hereto.

[ ] was filed on _____ as Application Serial No. _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Ezra Sutton, Reg. No. 25,770

Address all telephone calls to _____ at telephone no. (732) 634-3520

Address all correspondence to EZRA SUTTON, P.A.
Plaza 9, 900 Route 9
Woodbridge, New Jersey 07095

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor EDWARD L. TOBINICK, M.D.

Inventor's signature _____ Date April 4, 2001

Residence Los Angeles, California 90095-6903 Citizenship United States of America

Post Office Address 100 UCLA Medical Plaza, Suite 205
Los Angeles, California 90095-6903

Full name of second joint inventor, if any _____

Second Inventor's signature _____ Date _____

Residence _____ Citizenship _____

Post Office Address _____

(Supply similar information and signature for third and subsequent joint inventors.)

US006419944B2

(12) **United States Patent**
Tobinick

(10) **Patent No.: US 6,419,944 B2**
(45) **Date of Patent: *Jul. 16, 2002**

(54) **CYTOKINE ANTAGONISTS FOR THE TREATMENT OF LOCALIZED DISORDERS**

(76) Inventor: **Edward L. Tobinick**, 100 UCLA Medical Plz. Suite 205, Los Angeles, CA (US) 90095-6903

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/826,976**

(22) Filed: **Apr. 5, 2001**

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/563,651, filed on May 2, 2000, which is a continuation-in-part of application No. 09/476,643, filed on Dec. 31, 1999, now Pat. No. 6,177,077, which is a continuation-in-part of application No. 09/275,070, filed on Mar. 23, 1999, now Pat. No. 6,015,557, which is a continuation-in-part of application No. 09/256,388, filed on Feb. 24, 1999, now abandoned.

(51) **Int. Cl.**[7] **A61F 13/00**

(52) **U.S. Cl.** **424/422**; 424/427; 424/434; 424/130.1; 424/134.1; 424/141.1; 424/142.1; 424/145.1; 435/7.1; 435/7.8; 514/885; 514/913; 514/914

(58) **Field of Search** 424/134.1, 424, 424/427, 434, 301, 141.1, 142.1, 145.1; 435/7.1, 7.8; 514/885, 913, 914

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,105,557 A	*	1/2000	Tobinick et al.	424/134
6,177,077 B1	*	1/2001	Tobinick	424/134.1
6,180,355 B1	*	1/2001	Alexander et al.	435/7.1

* cited by examiner

Primary Examiner—Thurman K. Page
Assistant Examiner—Lakshmi Channavajjala
(74) *Attorney, Agent, or Firm*—Ezra Sutton

(57) **ABSTRACT**

Cytokine antagonists for use in localized clinical disorders are provided for the treatment and prevention of damage to the optic nerve, other cranial nerves, spinal cord, nerve roots, peripheral nerves or muscles caused by any one of the following: a herniated nucleus pulposus, osteoarthritis, other forms of arthritis, disorders of bone, disease, or trauma. The cytokine antagonists are used to treat these disorders by local administration. These cytokine antagonists include antagonists to tumor necrosis factor; interleukin-1; interleukin-6; and interleukin-8.

38 Claims, No Drawings

CYTOKINE ANTAGONISTS FOR THE TREATMENT OF LOCALIZED DISORDERS

RELATED APPLICATIONS

This is a continuation-in-part of application Ser. No. 09/563,651, filed on May 2, 2000, which is a continuation-in-part of Application Ser. No. 09/476,643, filed on Dec. 31, 1999, now U.S. Pat. No. 6,177,077, which is a continuation-in-part of application Ser. No. 09/275,070, filed on Mar. 23, 1999, now U.S. Pat. No. 6,015,557, which is a continuation-in-part of application Ser. No. 09/256,388, filed on Feb. 24, 1999, now abandoned.

FIELD OF THE INVENTION

The present invention relates to specific cytokine antagonists which are provided for the treatment and prevention of damage to the optic nerve, other cranial nerves, brain, spinal cord, nerve roots, peripheral nerves or muscles caused by any one of the following: a herniated nucleus pulposus, osteoarthritis, other forms of arthritis, disorders of bone, disease, or trauma. More particularly, the cytokine antagonists are used in a new treatment of these disorders utilizing localized anatomic administration which causes inhibition of the action of the corresponding pro-inflammatory cytokine in a localized anatomic area of the human body. The administration of these cytokine antagonists is performed by anatomically localized administration which includes, but is not limited to the following routes: perilesional; intralesional; and transconjunctival (for disorders of the optic nerve). Perilesional routes as mentioned above include, but are not limited to, subcutaneous, intramuscular, and epidural routes of administration.

BACKGROUND OF THE INVENTION

Localized administration for the treatment of localized clinical disorders has many clinical advantages over the use of conventional systemic treatment. Locally administered medication after delivery diffuses through local capillary, venous, arterial, and lymphatic action to reach the anatomic site of neurologic or muscular dysfunction; or in the case of the eye through the conjunctiva, then through the aqueous and vitreous humor to reach the optic nerve and retina.

All of the cytokine antagonists which are currently available have been developed for systemic administration. This is because all were developed to treat systemic illnesses, including rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, and Crohn's Disease. Systemic illnesses by definition require systemic treatment.

The use of cytokine antagonists to treat localized disorders is discussed in U.S. Pat. Nos. 6,015,557 and 6,177,077 and other pending applications of the applicant. This invention includes further applications of these ideas.

Localized administration, including perilesional or intralesional administration, when compared to systemic administration, carries with it one or more of the following advantages:

1) greater efficacy due to the achievement of higher local concentration;
2) greater efficacy due to the ability of the administered therapeutic molecule to reach the target tissue without degradation caused by hepatic or systemic circulation;
3) more rapid onset of action;
4) longer duration of action; and
5) Potentially fewer side effects, due to lower required dosage.

Pilot studies conducted by the inventor for one of the disorders discussed herein, herniated nucleus pulposus, have demonstrated the dramatic efficacy, and the extraordinarily rapid onset of action of perilesional administration in this clinical disorder. Ongoing pilot studies for other clinical conditions also demonstrate positive results.

Neurological disorders due to a herniated nucleus pulposus, osteoarthritis, other forms of arthritis, disorders of bone, disease, or trauma causing damage to the optic nerve, other cranial nerves, spinal cord, nerve roots, or peripheral nerves are common and cause considerable morbidity in the general population. Common to all of these disorders is the fact that they can cause permanent neurological damage, that damage can occur rapidly and be irreversible, and that current treatment of these conditions by pharmacologic or other means is often unsatisfactory. Surgical treatment is therefore often required, and is not uniformly successful.

Of these neurological disorders, radiculopathy due to a herniated nucleus pulposus is among the most common. This condition occurs in both the lumbar and cervical regions. Lumbar radiculopathy due to the herniation of a lumbar intervertebral disc causes sciatica i.e. pain in the lower back with radiation to a leg. Neurologic symptoms and signs are often present, including numbness, paresthesia, and motor symptoms involving the leg or foot. Cervical radiculopathy caused by a herniated nucleus pulposus in the cervical region causes pain and neurologic symptoms in the neck and an upper extremity. Other localized neurological conditions include acute spinal cord trauma, spinal cord compression, spinal cord hematoma, cord contusion (these cases are usually traumatic, such as motorcycle accidents or sports injuries); acute or chronic spinal cord compression from cancer (this is usually due to metastases to the spine, such as from prostate, breast or lung cancer); and carpal tunnel syndrome. Localized disorders of the cranial nerves include Bell's Palsy; and glaucoma, caused by glaucomatous degeneration of the optic nerve.

Pharmacologic agents used in the past to treat these disorders have included corticosteroids. Corticosteroid administration, however, may cause multiple side effects, and is often ineffective.

Newer biopharmaceutical medications have been developed which have been shown to offer dramatic clinical benefit for systemic illnesses in humans, even for those disorders which have not responded to large and repeated doses of corticosteroids. These biopharmaceutical medications fall into the category of cytokine antagonists because they block, or antagonize, the biologic action of a specific cytokine which has adverse clinical effects. These cytokines include members of the interleukin class and tumor necrosis factor.

Tumor necrosis factor (TNF) is intimately involved in the nervous system and in inflammatory disorders of muscle. It is central to the response to injury, either virally induced, disease induced, or occurring as a result of mechanical trauma. TNF is also central to neuronal apoptosis, a process important in many neurological disorders.

Specific inhibitors of TNF, only recently commercially available, now provide the possibility of therapeutic intervention in TNF mediated disorders. These agents have been developed to treat systemic illnesses, and therefore have been developed for systemic administration. Various biopharmaceutical companies have developed TNF antagonists to treat systemic illnesses: Immunex Corporation developed etanercept (Enbrel®) to treat rheumatoid arthritis; Johnson and Johnson developed infliximab (Remicade®) to treat Crohn's Disease and rheumatoid arthritis; D2E7, a human

Interleukin antagonists are administered in a therapeutically effective dose. Dosage interval varies from once per day to once per month for the subcutaneous, intramuscular, and epidural routes; and from TID to once per month for the transconjunctival route.

ADVANTAGES OF THE PRESENT INVENTION

Accordingly, an advantage of the present invention is that it provides for the localized administration of cytokine antagonists as a new pharmacologic treatment of localized disorders of components of the neurological system, optic nerve, or muscles; such that the use of these cytokine antagonists will result in the amelioration of these conditions.

Another advantage of the present invention is that it provides for cytokine antagonists by anatomically localized administration, which, when compared to systemic administration, produces one or more of the following: greater efficacy; more rapid onset; longer duration of action; or fewer side effects.

Another advantage of the present invention is that it provides for cytokine antagonists for providing suppression and inhibition of the action of cytokines in a human to treat localized neurological injury, trauma, disease, or compression; glaucoma; and muscular diseases.

Another advantage of the present invention is that it provides for cytokine antagonists that reduce inflammation by inhibiting the action of cytokines in the human body for the immediate, short term (acute conditions) and long term (chronic conditions), such that this reduction in inflammation will produce clinical improvement in the patient and will give the patient a better opportunity to heal, slow disease progression, prevent neurological damage, prevent optic nerve and muscular damage, or otherwise improves the patient's health.

Another advantage of the present invention is that it provides for cytokine antagonists, using localized administration, including perilesional or intralesional administration, as the preferred form of administration, for the treatment of localized neurological injury, trauma, disease, or compression; glaucoma; and muscular diseases.

A latitude of modification, change, and substitution is intended in the foregoing disclosure, and in some instances, some features of the invention will be employed without a corresponding use of other features. Accordingly, it is appropriate that the appended claims be construed broadly and in a manner consistent with the spirit and scope of the invention herein.

What is claimed is:

1. A method for inhibiting the action of TNF for treating neurological conditions in a human by administering a TNF antagonist for reducing the inflammation of neuronal tissue of said human, or for modulating the immune response affecting neuronal tissue of said human, comprising the steps of:

a) administering a therapeutically effective dosage level to said human of said TNF antagonist selected from the group consisting of a fusion protein identified as etanercept, infliximab, CDP571 (a humanized monoclonal anti-TNF-alpha IgG4 antibody), CDP 870 (a humanized monoclonal anti-TNF-alpha antibody fragment) and D2E7 (a human anti-TNF mAb) for reducing the inflammation of neuronal tissue of said human, or for modulating the immune response affecting neuronal tissue of said human; and

b) administering said dose either intralesionally or perilesionally.

2. A method for inhibiting the action of TNF in accordance with claim **1**, wherein the step of administering said dosage level is for treating Alzheimer's Disease.

3. A method for inhibiting the action of TNF in accordance with claim **1**, wherein the step of administering said TNF antagonist is performed through any of the following routes: subcutaneous, intrathecal, intramuscular, intranasal, transepidermal, parenteral, transconjunctival, or epidural.

4. A method for inhibiting the action of TNF in accordance with claim **1**, wherein the step of administering said dosage level is for treating nerve root injury caused by a herniated nucleus pulposus.

5. A method for inhibiting the action of TNF in accordance with claim **1**, wherein the step of administering said dosage level is for treating Bell's Palsy.

6. A method for inhibiting the action of TNF in accordance with claim **1**, wherein the step of administering said dosage level is for treating Carpal Tunnel Syndrome.

7. A method for inhibiting the action of TNF in accordance with claim **1**, wherein the step of administering said dosage level is for treating acute spinal cord injury.

8. A method for inhibiting the action of TNF in accordance with claim **1**, wherein the step of administering said dosage level is for treating spinal cord compression.

9. A method for inhibiting the action of TNF in accordance with claim **1**, wherein the step of administering said dosage level is for treating spinal stenosis.

10. A method for inhibiting the action of TNF in accordance with claim **1**, wherein the step of administering said dosage level is for treating localized disorders of muscle, including muscle spasm, muscle tear, muscle injury, muscle strain, or muscle sprain.

11. A method for inhibiting the action of TNF in accordance with claim **1**, wherein the step of administering said dosage level is for treating glaucoma.

12. A method for inhibiting the action of TNF in accordance with claim **1**, wherein the step of administering said TNF antagonist is performed subcutaneously in said human wherein said dosage level is in the range of 1 mg to 300 mg per dose.

13. A method for inhibiting the action of TNF in accordance with claim **1**, wherein the step of administering said TNF antagonist in the form of etanercept is performed intramuscularly in said human wherein said dosage level is in the range of 1 mg to 100 mg.

14. A method for inhibiting the action of TNF in accordance with claim **1**, wherein the step of administering said TNF antagonist in the form of etanercept is performed subcutaneously in said human wherein said dosage level is in the range of 1 mg to 100 mg.

15. A method for inhibiting the action of TNF in accordance with claim **1**, wherein the step of administering said TNF antagonist in the form of etanercept is performed subcutaneously in said human wherein said dosage level is in the range of 10 mg to 25 mg.

16. A method for inhibiting the action of TNF in accordance with claim **1**, wherein the step of administering said TNF antagonist in the form of D2E7 is performed subcutaneously in said human, wherein said dosage level is in the range of 1 mg to 100 mg.

17. A method for inhibiting the action of TNF in accordance with claim **1**, wherein the step of administering said TNF antagonist in the form of D2E7 is performed subcutaneously in said human, wherein said dosage level is in the range of 10 mg to 40 mg.

18. A method for inhibiting the action of TNF for treating or preventing nerve root injury in a human by administering

a TNF antagonist for reducing the inflammation of neuronal tissue of said nerve root of said human, or for modulating the immune response affecting neuronal tissue of said nerve root of said human, comprising the steps of:

a) administering a therapeutically effective dosage level to said human of etanercept, for reducing the inflammation of said nerve root of said human, or for modulating the immune response affecting neuronal tissue of said human; and

b) administering said dose either intralesionally or perilesionally.

19. A method for inhibiting the action of TNF for treating or preventing nerve root injury in a human by administering a TNF antagonist for reducing the inflammation of neuronal tissue of said nerve root of said human, or for modulating the immune response affecting neuronal tissue of said nerve root of said human, comprising the steps of:

a) administering a therapeutically effective dosage level to said human of etanercept, for reducing the inflammation of said nerve root of said human, or for modulating the immune response affecting neuronal tissue of said human; and

b) administering said dose subcutaneously to the area anatomically adjacent to the site of disc herniation.

20. A method for inhibiting the action of TNF in accordance with claim **19**, wherein the step of administering said dosage level is for treating nerve root injury due to a herniated nucleus pulposus, wherein the dosage level is between 1 mg and 100 mg.

21. A method for inhibiting the action of TNF for treating or preventing nerve root injury in a human by administering a TNF antagonist for reducing the inflammation of neuronal tissue of said nerve root of said human, or for modulating the immune response affecting neuronal tissue of said nerve root of said human, comprising the steps of:

a) administering a therapeutically effective dosage level to said human of said TNF antagonist selected from the group consisting of etanercept, infliximab, CDP571 (a humanized monoclonal anti-TNF-alpha IgG4 antibody), CDP 870 (a humanized monoclonal anti-TNF-alpha antibody fragment) and D2E7 (a human anti-TNF mAb), for reducing the inflammation of said nerve root of said human, or for modulating the immune response affecting neuronal tissue of said human; and

b) administering said dose either intralesionally or perilesionally.

22. A method for inhibiting the action of TNF for treating glaucoma in a human by administering a TNF antagonist for reducing the inflammation of the optic nerve or retina of said human, or for modulating the immune response affecting the optic nerve or retina of said human, comprising the step of:

a) administering a therapeutically effective dosage level to said human of said TNF antagonist selected from the group consisting of etanercept, infliximab, CDP571 (a humanized monoclonal anti-TNF-alpha IgG4 antibody), CDP 870 (a humanized monoclonal anti-TNF-alpha antibody fragment) and D2E7 (a human anti-TNF mAb) for treating glaucoma by reducing the inflammation of the optic nerve or retina of said human, or for modulating the immune response affecting the optic nerve or retina of said human.

23. A method for inhibiting the action of TNF in accordance with claim **22**, wherein the step of administering said TNF antagonist is performed through any of the following routes: subcutaneous, intranasal, transepidermal, parenteral, or transconjunctival.

24. A method for inhibiting the action of interleukin (IL) for treating neurological disorders in a human by administering an IL Blocker for reducing the inflammation of neuronal tissue of said human, or for modulating the immune response affecting neuronal tissue of said human, comprising the step of:

a) administering a therapeutically effective dosage level to said human of said IL Blocker for reducing the inflammation of neuronal tissue of said human, or for modulating the immune response affecting neuronal tissue of said human; and

b) administering said dose either intralesionally or perilesionally.

25. A method for inhibiting the action of IL in accordance with claim **24**, wherein said IL Blocker is selected from the group consisting of IL-1 RA, IL-1R type II, a monoclonal antibody to IL-1, soluble receptors to IL-1, soluble receptors to IL-1 fused to an F_c immunoglobulin fragment, a monoclonal antibody to IL-6, and a monoclonal antibody to IL-8.

26. A method for inhibiting the action of IL in accordance with claim **25**, wherein the step of administering said IL Blocker is performed through local subcutaneous administration for treating nerve root injury caused by intervertebral disc herniation.

27. A method for inhibiting the action of IL in accordance with claim **25**, wherein the step of administering said IL Blocker is performed through local subcutaneous administration for treating Bell's Palsy.

28. A method for inhibiting the action of IL in accordance with claim **25**, wherein the step of administering said IL Blocker is performed through local subcutaneous administration for treating acute spinal cord injury.

29. A method for inhibiting the action of IL in accordance with claim **25**, wherein the step of administering said IL Blocker is performed through the transconjunctival route via eye drops for treating glaucoma.

30. A method for inhibiting the action of TNF for treating or preventing nerve root injury in a human by administering a TNF antagonist for reducing the inflammation of neuronal tissue of said nerve root of said human, or for modulating the immune response affecting neuronal tissue of said nerve root of said human, comprising the steps of:

a) administering a therapeutically effective dosage level to said human of etanercept, for reducing the inflammation of said nerve root of said human, or for modulating the immune response affecting neuronal tissue of said human; and

b) administering said dose perilesionally by subcutaneous administration in the lumbar area (for lumbar or sacral nerve roots) or in the cervical area (for cervical nerve roots).

31. A method for inhibiting the action of TNF for treating or preventing nerve root injury in a human by administering a TNF antagonist for reducing the inflammation of neuronal tissue of said nerve root of said human, or for modulating the immune response affecting neuronal tissue of said nerve root of said human, comprising the steps of:

a) administering a therapeutically effective dosage level to said human of D2E7, for reducing the inflammation of said nerve root of said human, or for modulating the immune response affecting neuronal tissue of said human; and

b) administering said dose perilesionally by subcutaneous administration in the lumbar area (for lumbar or sacral nerve roots) or in the cervical area (for cervical nerve roots).

32. A method for inhibiting the action of TNF for treating or preventing nerve root injury in a human by administering a TNF antagonist for reducing the inflammation of neuronal tissue of said nerve root of said human, or for modulating the immune response affecting neuronal tissue of said nerve root of said human, comprising the steps of:

a) administering a therapeutically effective dosage level to said human of infliximab, for reducing the inflammation of said nerve root of said human, or for modulating the immune response affecting neuronal tissue of said human; and

b) administering said dose perilesionally by subcutaneous administration in the lumbar area (for lumbar or sacral nerve roots) or in the cervical area (for cervical nerve roots).

33. A method for inhibiting the action of TNF for treating or preventing nerve root injury in a human by administering a TNF antagonist for reducing the inflammation of neuronal tissue of said nerve root of said human, or for modulating the immune response to affecting neuronal tissue of said nerve root of said human, comprising the steps of:

a) administering a therapeutically effective dosage level to said human of CDP 870, for reducing the inflammation of said nerve root of said human, or for modulating the immune response affecting neuronal tissue of said human; and

b) administering said dose perilesionally by subcutaneous administration in the lumbar area (for lumbar or sacral nerve roots) or in the cervical area (for cervical nerve roots).

34. A method for inhibiting the action of TNF for treating or preventing nerve root injury in a human by administering a TNF antagonist for reducing the inflammation of neuronal tissue of said nerve root of said human, or for modulating the immune response affecting neuronal tissue of said nerve root of said human, comprising the steps of:

a) administering a therapeutically effective dosage level to said human of CDP 571, for reducing the inflammation of said nerve root of said human, or for modulating the immune response affecting neuronal tissue of said human; and

b) administering said dose perilesionally by subcutaneous administration in the lumbar area (for lumbar or sacral nerve roots) or in the cervical area (for cervical nerve roots).

35. A method for inhibiting the action of TNF for treating neurological conditions in a human by administering a TNF antagonist for reducing the inflammation of neuronal tissue of said human, or for modulating the immune response affecting neuronal tissue of said human, comprising the step of:

a) administering a therapeutically effective dosage level to said human of said TNF antagonist selected from the group consisting of a fusion protein identified as etanercept, infliximab, CDP57 1 (a humanized monoclonal anti-TNF-alpha IgG4 antibody), CDP 870 (a humanized monoclonal anti-TNF-alpha antibody fragment)and D2E7 (a human anti-TNF mAb) for reducing the inflammation of neuronal tissue of said human, or for modulating the immune response affecting neuronal tissue of said human.

36. A method for inhibiting the action of TNF in accordance with claim 35, wherein the step of administering said dosage level is for treating Alzheimer's Disease.

37. A method for inhibiting the action of TNF in accordance with claim 35, wherein the step of administering said dosage level is for treating glaucoma.

38. A method for inhibiting the action of TNF in accordance with claim 35, wherein the step of administering said dosage level is for treating Postherpetic Neuralgia.

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TNF INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS

RELATED APPLICATION

application is a divisional of 09/476,643, filed December 31, 1999, now U.S. Patent 6,177,077, which

This is a continuation-in-part of Application Serial No. 09/256,388, filed on February 24, 1999, now abandoned.

11/15/01

FIELD OF THE INVENTION

The present invention relates to tumor necrosis factor (TNF) antagonists or TNF blockers for the treatment of neurological disorders, trauma, injuries or compression; demyelinating neurological disorders, including multiple sclerosis; neurodegenerative diseases, including Alzheimer's disease; muscular disorders; and disorders of the optic nerve and retina (hereinafter "Neurologic and Related TNF Disorders"). More particularly, the TNF antagonists, TNF inhibitors or TNF blockers, are used for the treatment, prevention or amelioration of these "Neurologic and Related TNF Disorders" by modulating the action of TNF in the human body. The use of these TNF antagonists or TNF blockers results in the amelioration of these disorders and diseases and represents a novel use for this class of drugs.

BACKGROUND OF THE INVENTION

Neurological disorders due to demyelinating disease (e.g. multiple sclerosis), immune disease, inflammation, trauma, or compression, occur in different clinical forms depending upon the anatomic site and the cause and natural history of the physiological problem. For example, in Alzheimer's disease the brain undergoes a serious form of neurodegeneration

of unknown etiology. Common to all of these disorders is the fact that they can cause permanent neurological damage, that damage can occur rapidly and be irreversible, and that current treatment of these conditions is unsatisfactory, often requiring surgery and/or the use of pharmacologic agents, which are often not completely successful.

These neurological conditions include acute spinal cord trauma, spinal cord compression, spinal cord hematoma, cord contusion (these cases are usually traumatic, such as motorcycle accidents or sports injuries); nerve compression, the most common condition being a herniated disc causing sciatic nerve compression, neuropathy, and pain; but also including cervical disc herniation, causing nerve compression in the neck; acute or chronic spinal cord compression from cancer (this is usually due to metastases to the spine, such as from prostate, breast or lung cancer); autoimmune disease of the nervous system; and demyelinating diseases, the most common condition being multiple sclerosis.

Steroid drugs such as cortisone that are used to treat many of the aforementioned neurological problems and conditions are particularly hazardous because they are used either at high dosage, with a corresponding increasing risk of side effects, or because they are used chronically, also increasing their adverse effects. Lastly, steroids are only partially effective or completely ineffective.

Tumor necrosis factor (TNF), a naturally occurring cytokine, plays a central role in the inflammatory response and in immune injury. TNF is formed by the cleavage of a precursor transmembrane protein, forming soluble molecules which aggregate to form

trimolecular complexes. These complexes then bind to receptors found on a variety of cells. Binding produces an array of pro-inflammatory effects, including release of other pro-inflammatory cytokines, including interleukin (IL)-6, IL-8, and IL-1; release of matrix metalloproteinases; and up regulation of the expression of endothelial adhesion molecules, further amplifying the inflammatory and immune cascade by attracting leukocytes into extravascular tissues. TNF is now well established as key in the pathogenesis of rheumatoid arthritis (RA) and Crohn's Disease.

Specific inhibitors of TNF, only recently commercially available, now provide the possibility of therapeutic intervention in TNF mediated diseases. Dramatic therapeutic success has already been demonstrated with infliximab, a chimeric anti-TNF monoclonal antibody (mAb), in treating Crohn's Disease and RA; and with etanercept, a recombinant fusion protein consisting of two soluble TNF receptors joined by the Fc fragment of a human IgG1 molecule, in treating RA and Psoriatic Arthritis. Other specific anti-TNF agents are under development, including D2E7 (a human anti-TNF mAb), CDP 571 (a chimeric, but 95% humanized, anti-TNF mAb), and a pegylated soluble TNF type 1 receptor. Additionally, thalidomide has been demonstrated to be a potent anti-TNF agent. Further, anti-TNF therapies may include gene therapy and the development of selective inhibitors of the TNF-alpha converting enzyme.

As with other organ systems, TNF has been shown to have a key role in the central nervous system. There is a need for TNF inhibitors that will open a new realm of therapeutic possibilities for a wide variety of neurological and related disorders. These disorders are diverse and include inflammatory and autoimmune disorders of the nervous system, including multiple sclerosis, Guillain Barre syndrome, and myasthenia gravis; degenerative disorders of the nervous system, including Alzheimer's disease, Parkinson's disease and Huntington's disease; disorders of related systems of the retina and of muscle, including optic neuritis, macular degeneration, diabetic retinopathy, dermatomyositis, amyotrophic lateral sclerosis, and muscular dystrophy; and injuries to the nervous system, including traumatic brain injury, acute spinal cord injury, and stroke.

The limited ability of the body to effect repair after injury to the nervous system, the devastating nature of these diseases and the lack of effective therapy all highlight the importance of early therapy aimed at preventing or limiting neuronal destruction. Anti-TNF therapies are ideally suited to this task because they have been demonstrated to dramatically limit inflammation by interrupting the inflammatory cascade at a fundamental level.

There remains a need for a new pharmacologic treatment of these aforementioned physiological problems of the nervous system associated with autoimmune disease, demyelinating diseases, neurodegenerative diseases, trauma, injuries and compression with the pharmacological use of TNF antagonists or TNF blockers, which are greatly beneficial for the large number of patients whom these conditions affect. Drugs which are powerful

TNF blockers are etanercept, infliximab, pegylated soluble TNF Receptor Type I (PEGs TNF-R1), other agents containing soluble TNF receptors, CDP571 (a humanized monoclonal anti-TNF-alpha antibodies), thalidomide, phosphodiesterase 4 (IV) inhibitor thalidomide analogues and other phosphodiesterase IV inhibitors. Etanercept or infliximab may be used for the immediate, short term and long term (acute and chronic) blockade of TNF in order to minimize neurological damage mediated by TNF dependent processes occurring in the aforementioned neurological disorders. The use of these TNF antagonists or TNF blockers would result in the amelioration of these physiological neurological problems.

Additionally, several of these TNF agents will not cross the blood-brain barrier. Accordingly, there is also a need for these TNF agents to be introduced directly into the cerebrospinal fluid to be effective. This can be accomplished either at the level of the spinal cord, or by introduction into the ventricular system of the brain, usually via an indwelling, subcutaneous reservoir which is connected by catheter into the ventricular system. This will allow the chronic use of these agents for the treatment of neurological disorders which require chronic TNF modulation.

DESCRIPTION OF THE PRIOR ART

Pharmacologic chemical substances, compounds and agents which are used for the treatment of neurological disorders, trauma, injuries and compression having various organic structures and metabolic functions have been disclosed in the prior art. For example, U.S. Patent Nos. 5,756,482 and 5,574,022 to ROBERTS et al disclose methods of attenuating

physical damage to the nervous system and to the spinal cord after injury using steroid hormones or steroid precursors such as pregnenolone, and pregnenolone sulfate in conjunction with a non-steroidal anti-inflammatory substance such as indomethacin. These prior art patents do not teach the use of a TNF antagonist or TNF blocker for the suppression and inhibition of the action of TNF in the human body to treat "Neurologic and Related TNF Disorders", as in the present invention.

U.S. Patent No. 5,605,690 to JACOBS discloses a method for treating TNF-dependent inflammatory diseases such as arthritis by administering a TNF antagonist, such as soluble human TNFR (a sequence of amino acids), to a human. This prior art patent does not teach the use of a TNF antagonist or TNF blocker for the suppression and inhibition of the action of TNF in the human body to treat "Neurologic and Related TNF Disorders", as in the present invention.

U.S. Patent No. 5,656,272 to LE et al discloses methods of treating TNF-alpha-mediated Crohn's disease using chimeric anti-TNF antibodies. This prior art patent does not teach the use of a TNF antagonist or TNF blocker for the suppression and inhibition of the action of TNF in the human body to treat "Neurologic and Related TNF Disorders", as in the present invention.

U.S. Patent No. 5,650,396 discloses a method of treating multiple sclerosis (MS) by blocking and inhibiting the action of TNF in a patient. This prior art patent does not teach the use of TNF antagonists as in the present invention.

None of the prior art patents disclose or teach the use of the TNF antagonists or TNF blockers of the present invention for suppression and inhibition of the action of TNF in a human to treat "Neurologic and Related TNF Disorders", in which the TNF antagonist gives the patient a better opportunity to heal, slows disease progression, prevents neurological damage, or otherwise improves the patient's health.

Accordingly, it is an object of the present invention to provide TNF antagonists for a new pharmacologic treatment of "Neurologic and Related TNF Disorders", such that the use of these TNF antagonists will result in the amelioration of these conditions.

Another object of the present invention is to provide a TNF antagonist for providing suppression and inhibition of the action of TNF in a human to treat "Neurologic and Related TNF Disorders".

Another object of the present invention is to provide a TNF antagonist that reduces inflammation to the patient by inhibiting the action of TNF in the human body for the immediate, short term (acute conditions) and long term (chronic conditions), such that this reduction in inflammation will produce clinical improvement in the patient and will give the patient a better opportunity to heal, slows disease progression, prevents neurological damage, or otherwise improves the patient's health.

Another object of the present invention is to provide TNF antagonists that can offer acute and chronic treatment regimens for neurological conditions caused by neurological trauma, compression, injury and/or disease; such conditions including acute spinal cord or

brain injury, herniated nucleus pulposus (herniated disc), spinal cord compression due to metastatic cancer, primary or metastatic brain tumors, chronic pain syndromes due to metastatic tumor, increased intracranial pressure, demyelinating diseases such as multiple sclerosis, neurodegenerative diseases such as Alzheimer's disease, inflammatory CNS disease, such as subacute sclerosing panencephalitis, and other related neurological disorders and diseases.

Another object of the present invention is to provide a TNF antagonist that can offer acute and chronic treatment regimens for neurological and related diseases. Examples of diseases in these categories include but are not limited to diseases of the central and peripheral nervous system such as Parkinson's disease, Bell's palsy, Guillain-Barre syndrome.

Another object of the present invention is to provide a TNF antagonist that can offer acute and chronic treatment for retinal and neuro-ophthalmic diseases. Examples of diseases in these categories include but are not limited to optic neuritis, macular degeneration and diabetic retinopathy.

Another object of the present invention is to provide a TNF antagonist that can offer acute and chronic treatment for muscular diseases and diseases of the neuromuscular junction. Examples of diseases in these categories include but are not limited to dermatomyositis, amyotrophic lateral sclerosis and muscular dystrophy.

Another object of the present invention is to provide a TNF antagonist that can offer acute and chronic treatment regimens for degenerative neurological disorders and neurologic disorders of uncertain etiology. Examples of diseases in these categories include but are not limited to Alzheimer's disease, Huntington's disease, and Creutzfeld-Jakob disease.

Another object of the present invention is to provide a TNF antagonist that can offer acute and chronic treatment regimens for neurologic injuries. Examples of diseases in these categories include but are not limited to acute spinal cord injury, acute brain injury, and stroke.

Another object of the present invention is to provide a TNF antagonist that can offer acute and chronic treatment regimens for inflammatory and autoimmune disorders of the nervous system, examples being subacute sclerosing panencephalitis and myasthenia gravis.

SUMMARY OF THE INVENTION

The present invention provides a method for inhibiting the action of TNF for treating neurological conditions in a human by administering a TNF antagonist for reducing the inflammation of neuronal tissue or the neuromuscular junction of a human, or for modulating the immune response affecting neuronal tissue or the neuromuscular junction of a human by administering to the human a therapeutically effective dosage level of a TNF antagonist. The TNF antagonist is selected from the group consisting of etanercept, infliximab, pegylated soluble TNF receptor Type I (PEGsTNF-R1), other agents containing soluble TNF receptors, CDP571 (a humanized monoclonal anti-TNF-alpha antibody), other monoclonal anti-TNF-

alpha antibodies, TNF-alpha converting enzyme inhibitors and D2E7 (a human anti-TNF mAb) for reducing the inflammation of neuronal tissue or the neuromuscular junction of a human, or for modulating the immune response affecting neuronal tissue or the neuromuscular junction of a human. Additionally, other TNF antagonists are used for administering a therapeutically effective dosage level to a human wherein the TNF antagonist is selected from the group consisting of thalidomide, phosphodiesterase 4 (IV) inhibitor thalidomide analogues and other phosphodiesterase IV inhibitors for reducing the inflammation of neuronal tissue or the neuromuscular junction of a human, or for modulating the immune response affecting neuronal tissue or the neuromuscular junction of a human.

The present invention further provides a method for inhibiting the action of TNF for treating conditions of the optic nerve or retina in a human by administering a TNF antagonist for reducing the inflammation of the optic nerve or retina of a human, or for modulating the immune response affecting the optic nerve or retina of a human by administering a therapeutically effective dosage level to the human of a TNF antagonist. The TNF antagonist is selected from the aforementioned pharmacological products listed above.

The present invention also provides a method for inhibiting the action of TNF for treating muscular diseases in a human by administering a TNF antagonist for reducing the inflammation of muscle of a human, or for modulating the immune response affecting the muscle of a human by administering a therapeutically effective dosage level to the human

of a TNF antagonist. The TNF antagonist is selected from the aforementioned pharmacological products listed above.

In the step of administering the TNF antagonist to a human, the TNF antagonist is performed through any of the following routes including subcutaneous, intravenous, intrathecal, intramuscular, intranasal, oral, transepidermal, parenteral, by inhalation, or intracerebroventricular.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

TNF antagonist regimens to be used for treating disorders are designed in two general ways: acute regimens, designed to achieve rapid blood levels and rapid action, wherein the TNF blockade is desired for hours to days; and chronic regimens, wherein the TNF blockade is desired for days, weeks, or months. TNF antagonists which are suitable for these regimens are etanercept (ENBREL™) from Immunex Corporation ; infliximab (REMICADE™) from Centocor, Inc.; pegylated soluble TNF Receptor Type I (PEGs TNF-R1); other agents containing soluble TNF receptors; CDP571 (a humanized monoclonal anti-TNF-alpha antibodies); other monoclonal anti-TNF-alpha antibodies; D2E7 (a human anti-TNF m Ab); thalidomide; phosphodiesterase 4 (IV) inhibitor thalidomide analogues; other phosphodiesterase IV inhibitors; and TNF alpha converting enzyme inhibitors. Etanercept or infliximab may be used for the immediate, short term and long term (acute and chronic) blockade of TNF in order to minimize neurological damage mediated by TNF dependent

processes occurring in the aforementioned "Neurologic and Related TNF disorders". The use of these TNF antagonists or TNF blockers results in the amelioration of these physiological problems.

Trauma, injury, compression and other neurological disorders can affect individual nerves, nerve roots, the spinal cord, or the brain. The conditions which are of most concern in the present invention are the following:

1) acute spinal cord and brain injury,

2) demyelinating diseases, such as multiple sclerosis,

3) spinal cord compression due to metastatic cancer,

4) primary or metastatic brain tumors,

5) chronic pain syndromes due to metastatic tumor,

6) inflammatory CNS diseases, such as subacute sclerosing panencephalitis,

7) Alzheimer's disease,

8) Huntington's disease,

9) Creutzfeld-Jakob disease,

10) Parkinson's disease,

11) myasthenia gravis,

12) Guillain-Barre syndrome,

13) Bell's palsy,

14) diabetic neuropathy,

15) amyotrophic lateral sclerosis,

16) optic neuritis,

17) macular degeneration,

18) retinitis pigmentosa,

19) diabetic retinopathy,

20) muscular dystrophy, and

21) polymyositis-dermatomyositis.

TNF antagonists are a novel way to treat the above-listed disorders in comparison with steroids. Experimental evidence has shown that excessive levels of TNF are released by injury to neuronal tissue. Accordingly, the use of TNF antagonists will result in amelioration of these disorders and diseases. Because of the profoundly powerful action of the new TNF antagonists that have recently become available, these agents can provide treatment in a unique way, filling an urgent clinical need for more effective therapy. Also, because of the extremely safe side effect profile of these agents, they can be used either singly or in combination with other pharmacologic agents. TNF antagonists can also safely be used with steroids, which are the only other class of agents which have been shown to be beneficial for certain of these conditions. Importantly, the TNF antagonists lack the adverse effects of steroids as previously described. Lastly, steroids are only partially effective or completely ineffective.

The TNF antagonists may be administered by any of the following methods to treat the above-identified disorders: subcutaneous, intravenous, intrathecal, intramuscular, intranasal, oral, transepidermal, parenteral, by inhalation, or intracerebroventricular. Also, the dosage regimens for treatment are of 3 types:

Regimen 1: Acute Regimen

This regimen can be used to treat all of the disorders listed above, with any of the TNF antagonists listed above, and with any of the routes of administration listed above. This regimen may include just a single dose, or repeated doses up to and including 30 continuous days.

Regimen 2: Chronic Regimen

This regimen can be used to treat all of the disorders listed above, except for: acute spinal cord and brain injury, spinal cord compression, and Bell's palsy. Any of the TNF antagonists listed above may be used, and any of the routes of administration listed above may be used. This regimen includes repeated doses of 31 days or longer.

Regimen 3: Directly Into The CSF

This regimen may be used for acute, chronic or both regimens. There are two variations: either through the intrathecal route at the level of the spinal cord; or directly into the cerebroventricular system at the level of the brain. This regimen can be used to treat all of the disorders listed above, except for: myasthenia gravis, Bell's palsy, diabetic neuropathy, and amyotrophic lateral sclerosis.

More detailed discussion of each of these clinical conditions is as follows:

1) Acute spinal cord and brain injury:

About 10,000 cases occur per year in the U.S., with a current population of over 200,000 patients with residual neurologic damage, many of whom are paralyzed (quadriplegia or paraplegia). Current treatment for the acute injury is inadequate. In the early 1990's it was shown that early (within 8 hours of injury) treatment with high doses of steroids (methyl prednisolone) was beneficial for some of these patients. Surgical stabilization and spinal decompression is often necessary because of excessive swelling (edema) which can itself cause further severe injury to the cord due to further compression of the cord against its bony spinal canal. The etiology of most of these cases are motor vehicle accidents, with the remainder being sports injuries, falls, and other accidents. The window of opportunity for treatment is small, since massive swelling can occur within minutes.

The treatment regimen used here would be the acute regimen. This could involve any of the TNF antagonists, but currently etanercept would be the leading candidate. Etanercept is currently approved only for rheumatoid arthritis, and is used as a subcutaneous injection of 25mg given twice a week. This regimen produces peak blood levels in an average of 72 hours. Preferred methods for acute spinal cord or brain injury involve either administration directly into the CSF or through intravenous infusion producing a therapeutic effect more rapidly than can be produced by subcutaneous injection. These are new methods of dosing

that are not being used for arthritis. These acute regimens are unique delivery methods for etanercept and are uniquely necessary for clinical neurologic conditions requiring rapid blockade of TNF.

Regimens 1 and 3, as outlined above, may be used to treat these disorders.

2) Demyelinating Disease, Such As Multiple Sclerosis:

Demyelinating neurological diseases, the most important being multiple sclerosis, are inadequately treated by currently available therapies, and continue to produce progressive, severe, neurologic impairment in a large population of patients in the United States and worldwide. There is experimental evidence which documents the role of TNF in multiple sclerosis. There is a wide body of work which documents the role of both cellular and humoral immunity in multiple sclerosis. Using the above-listed TNF antagonists represents a novel approach to the treatment of these important disorders.

Several novel approaches are suggested. For acute demyelinating disease, it is paramount to use therapy which is rapidly effective to prevent permanent neurological damage. In this case, novel routes of administration of the TNF antagonists may be used. These novel routes include administration of etanercept or infliximab directly into the CSF; or intravenous administration of etanercept. For chronic forms of demyelinating disease, the more familiar routes of administration of etanercept (subcutaneous) or infliximab (intravenous) may be elected. These novel regimens are designed as such because of the complementary mechanisms of action and low toxicity of these biopharmaceutical agents.

Regimens 1, 2 and 3, as outlined above, may be used to treat these disorders.

3) Spinal cord compression due to metastatic cancer:

Cord compression due to metastatic cancer is a catastrophic event leading to rapid paralysis if not quickly diagnosed and treated. It is most common with cancers of the breast, colon, lung and prostate, but can be a complication of metastatic disease from a wide variety of malignancies, including melanoma and multiple myeloma. Current treatment regimens include high dose steroids, emergency radiation treatment, and/or emergent surgical decompression. Paralysis can occur within hours, so treatment must be initiated within this time period to avoid permanent sequelae. The mechanism of action of TNF blockage here would be similar to that above. In addition, it is possible that TNF blockade could be directly tumoricidal or tumoristatic with certain malignancies. Impending cord compression could be treated with the chronic regimen. However, as explained above, most patients would need to be emergently treated with the acute regimen, as outlined above.

Regimens 1 and 3, as outlined above, may be used to treat these disorders.

4) Primary or Metastatic Brain Tumors:

Primary brain tumors can be either benign (most commonly meningioma) or malignant (usually gliomas). Metastatic brain tumors can be from any source, most commonly lung cancer, breast cancer, or other malignancies such as melanoma. Treatment for these tumors is primarily surgery or radiation, with generally poor response to chemotherapy. Many of these tumors cause surrounding edema which can cause further

neurologic deterioration. TNF blockade, either the acute or chronic treatment regimen, would be beneficial while these patients are awaiting surgery. Additionally, TNF blockade, as discussed above, would have direct tumor inhibiting properties.

Regimens 1, 2 and 3, as outlined above, may be used to treat these disorders.

5) Chronic pain syndromes due to metastatic tumor:

Pain due to metastatic cancer is inadequately treated by currently used agents. It is probable that the mechanism of action of this pain is mediated in part by the overproduction of TNF. TNF blockade would be beneficial for selected tumors, particularly bone metastases where compression is involved. The chronic treatment regimens would be used. One general note of caution when treating malignancies is necessary: While TNF blockade is likely to have an antitumor effect with certain malignancies, it is also possible that TNF blockade could increase growth rates with certain malignancies.

Regimens 1, 2 and 3, as outlined above, may be used to treat these disorders.

6) Inflammatory CNS Diseases, Such As Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis is a rare inflammatory disease of the brain, secondary to infection with a measles virus.

Regimens 1, 2 and 3, as outlined above, may be used to treat these disorders.

7) Alzheimer's Disease

Alzheimer's disease is a common form of progressive dementia, of unknown cause and without an effective cure. It is characterized by neurofibrillary tangles and plaques on pathologic examination of brain tissue.

Regimens 1, 2 and 3, as outlined above, may be used to treat these disorders.

8) Huntington's Disease

Huntington's disease (Huntington's chorea) is a rare, progressive, fatal neurological disorder for which there is currently no effective treatment. It is often hereditary, and is characterized by a movement disorder (chorea), as well as progressive dementia.

Regimens 1, 2 and 3, as outlined above, may be used to treat these disorders.

9) Creutzfeld-Jakob Disease

Creutzfeld-Jakob disease, as well as New Variant Creuzfeld-Jakob disease, is one of the transmissible spongioform encephalopathies, along with Kuru and Scrapie and "Mad Cow Disease (Bovine spongioform encephalopathy)". These diseases are caused by infection with a new class of biologic agent called prions. These diseases are progressive, fatal, and can be contracted by ingesting tissue of an infected animal. There is no known treatment.

Regimens 1, 2 and 3, as outlined above, may be used to treat these disorders.

10) Parkinson's Disease

Parkinson's disease is a common neurologic disorder characterized by tremor, gait disorder, and dementia, for which there is no known cure.

Regimens 1, 2 and 3, as outlined above, may be used to treat these disorders.

11) Myasthenia Gravis

Myasthenia gravis is an autoimmune disorder of the neuromuscular junction, characterized by muscle weakness and easy fatiguability. There is no known cure. Corticosteroids are one of the mainstays of treatment.

Regimens 1 and 2, as outlined above, may be used to treat these disorders.

12) Guillain-Barre Syndrome

Guillain-Barre syndrome is characterized by the rapid onset of weakness, usually in an ascending distribution, and often culminating in difficulty breathing. It often follows a preceding viral infection.

Regimens 1, 2 and 3, as outlined above, may be used to treat these disorders.

13) Bell's Palsy

Bell's palsy is characterized by the sudden onset of hemifacial paralysis, caused by acute mononeuropathy of the seventh cranial nerve, the facial nerve. It can follow viral infection, vaccination, or may be idiopathic. The mainstay of treatment is large doses of corticosteroids.

Regimen 1, as outlined above, may be used to treat this disorder.

14) Diabetic Neuropathy

Diabetic neuropathy consists of a variety of clinical syndromes of neurologic damage occurring in patients with either juvenile onset or adult onset diabetes mellitus. Diabetic peripheral neuropathy causes sensory deficits, numbness, tingling, and painful paresthesias in the extremities. Diabetic autonomic neuropathy causes disorders of the autonomic nervous system, including diabetic gastropathy.

Regimens 1 and 2, as outlined above, may be used to treat these disorders.

15) Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis is a progressive fatal, neurologic disease causing progressive weakness and cranial nerve palsies, causing difficulty with speech, eye movements, and such. There is no known cure.

Regimens 1 and 2, as outlined above, may be used to treat these disorders.

16) Optic Neuritis

Optic neuritis is characterized by acute inflammation affecting the optic nerve, causing visual field defects. It is often part of Multiple Sclerosis, for which it may be the presenting symptom. Attacks can be intermittent and repeated.

Regimens 1, 2 and 3, as outlined above, may be used to treat these disorders.

17) Macular Degeneration

Macular degeneration is a leading cause of blindness, affecting predominantly the older population, for which there is no known cure.

Regimens 1, 2 and 3, as outlined above, may be used to treat these disorders.

18) Retinitis Pigmentosa

Retinitis pigmentosa is a hereditary retinal disease, resulting in blindness, for which there is no known cure.

Regimens 1, 2 and 3, as outlined above, may be used to treat these disorders.

19) Diabetic Retinopathy

Diabetic Retinopathy includes a spectrum of retinal disorders, including hemorrhage and exudates, which occur in patients with diabetes mellitus. Part of the retinopathy is due to a vascular damage caused by diabetes.

Regimens 1, 2 and 3, as outlined above, may be used to treat these disorders.

20) Muscular Dystrophy

Muscular dystrophy is a group of related diseases of muscle, many of which are hereditary, characterized by progressive muscular weakness. The cause and cure are unknown.

Regimens 1 and 2, as outlined above, may be used to treat these disorders.

21) Polymyositis - Dermatomyositis

Polymyositis is an autoimmune inflammatory disease of muscle, characterized by progressive proximal muscle weakness and muscle wasting. Pathology shows an intense inflammatory infiltrate in the muscle. Treatment includes immunosuppressive drugs, corticosteroids, and respiratory support for more advanced cases. Dermatomyositis is polymyositis with a characteristic accompanying skin rash.

Regimens 1 and 2, as outlined above, may be used to treat these disorders.

METHODS OF ADMINISTRATION AND DOSAGE LEVELS

For treating the above diseases with the above mentioned TNF antagonists, these TNF antagonists may be administered by the following routes:

The above TNF antagonists may be administered subcutaneously in the human and the dosage level is in the range of 5mg to 50mg for acute or chronic regimens.

The above TNF antagonists may be administered intranasally in the human and the dosage level is in the range of 0.1mg to 10mg for acute or chronic regimens.

The above TNF antagonists may be administered intramuscularly in the human and the dosage level is in the range of 25mg to 100mg.

The above TNF antagonists may be administered intravenously in the human and the dosage level is in the range of 2.5mg/kg to 20mg/kg.

The above TNF antagonists may be administered intrathecally in the human and the dosage level is in the range of 0.1mg to 25mg administered from once a day to every three months.

The above TNF antagonists may be administered transepidermally in the human and the dosage level is in the range of 10mg to 100mg.

The above TNF antagonists may be administered by inhaling by the human and the dosage level is in the range of 0.2mg to 40mg.

The above TNF antagonists may be administered intracerebroventricularly in the human and the dosage level is in the range of 0.1mg to 25mg administered once a day to once every 3 month.

The above TNF antagonists may be administered orally by the human and the dosage level is in the range of 10mg to 300mg.

Etanercept is administered intramuscularly in a human wherein the dosage level is in the range of 25mg to 100mg.

Infliximab is administered intravenously in a human wherein the dosage level is in the range of 2.5mg/kg to 20mg/kg.

Etanercept is administered subcutaneously in a human wherein the dosage level is in the range of 5mg to 50mg.

Etanercept is administered intrathecally in a human wherein the dosage level is in the range of 0.1mg to 25mg administered from once a day to once a month.

Infliximab is administered intrathecally in a human wherein the dosage level is in the range of 0.1mg/kg to 5mg/kg administered from once a week to once every three months.

Etanercept is administered intracerebroventricularly in a human wherein the dosage level is in the range of 0.1mg to 25mg administered once a day to once a month.

Infliximab is administered intracerebroventricularly in a human wherein the dosage level is in the range of 0.1mg/kg to 5mg/kg administered once a week to once every 3 months.

The thalidomide group is administered orally by a human wherein the dosage level is in the range of 10mg to 300mg.

All antagonists and all routes of administration can be used for all of the above diseases with the following exceptions:

a) Etanercept and infliximab will only be used subcutaneously, intramuscularly, intraventricularly, or intrathecally, or intravenously.

b) Intracerebroventricular and intrathecal routes are more invasive, and will only be used with severe disorders, usually only with those that are fatal or devastating. As to the diseases and disorders discussed above, these routes are most suitable for acute brain and spinal cord injury; Alzheimer's disease; subacute sclerosing panencephalitis; Parkinson's disease; Huntington's disease; Creutzfeld-Jakob disease; amyotrophic lateral sclerosis; myasthenia gravis; optic neuritis; multiple sclerosis; macular degeneration, and retinitis pigmentosa. Excluded are diseases outside of the CNS, i.e. those involving muscle or

peripheral nerves. These excluded diseases include diabetic neuropathy; Bell's palsy (too mild to justify this route), muscular dystrophies; and polymyositis.

c) All other routes should be specified for all of the diseases, except that the thalidomide group will not be used for diabetic neuropathy or for peripheral neuropathy.

ADVANTAGES OF THE PRESENT INVENTION

Accordingly, an advantage of the present invention is that it provides TNF antagonists for a new pharmacologic treatment of "Neurologic and Related TNF Disorders", such that the use of these TNF antagonists will result in the amelioration of these conditions.

Another advantage of the present invention is that it provides for a TNF antagonist, for providing suppression and inhibition of the action of TNF in a human to treat "Neurologic and Related TNF Disorders".

Another advantage of the present invention is that it provides for a TNF antagonist that reduces inflammation to the patient by inhibiting the action of TNF in the human body for the immediate, short term (acute conditions) and long term (chronic conditions), such that this reduction in inflammation will produce clinical improvement in the patient and will give the patient a better opportunity to heal, slows disease progression, prevents neurological damage, or otherwise improves the patient's health.

Another advantage of the present invention is that it provides TNF antagonists that can offer acute and chronic treatment regimens for neurological conditions caused by neurological trauma, compression, injury and/or disease; such conditions including acute spinal cord injury, spinal cord compression due to metastatic cancer, primary or metastatic brain tumors, chronic pain syndromes due to metastatic tumor, increased intracranial pressure, demyelinating diseases such as multiple sclerosis, neurodegenerative diseases such as Alzheimer's disease, inflammatory CNS disease, such as subacute sclerosing panencephalitis, and other related neurological disorders and diseases.

Another advantage of the present invention is that it provides for a TNF antagonist that can offer acute and chronic treatment regimens for neurologic and related diseases. Examples of diseases in these categories include but are not limited to diseases of the central and peripheral nervous system such as Parkinson's disease, Bell's palsy, Guillain-Barre Syndrome.

Another advantage of the present invention is that it provides for a TNF antagonist that can offer acute and chronic treatment for retinal and neuro-ophthalmic diseases. Examples of diseases in these categories include but are not limited to optic neuritis, macular degeneration and diabetic retinopathy.

Another advantage of the present invention is that it provides for a TNF antagonist that can offer acute and chronic treatment for muscular diseases and diseases of the neuromuscular junction. Examples of diseases in these categories include but are not limited to dermatomyositis, amyotrophic lateral sclerosis and muscular dystrophy.

Another advantage of the present invention is that it provides for a TNF antagonist that can offer acute and chronic treatment regimens for degenerative neurologic disorders and neurologic disorders of uncertain etiology. Examples of diseases in these categories include but are not limited to Alzheimer's disease, Huntington's disease, and Creutzfeld-Jakob disease.

Another advantage of the present invention is that it provides for a TNF antagonist that can offer acute and chronic treatment regimens for neurologic injuries. Examples of diseases in these categories include but are not limited to acute spinal cord injury, acute brain injury, and stroke.

Another advantage of the present invention is that it provides for a TNF antagonist that can offer acute and chronic treatment regimens for inflammatory and autoimmune disorders of the nervous system, examples being subacute sclerosing panencephalitis and myasthenia gravis.

A latitude of modification, change, and substitution is intended in the foregoing disclosure, and in some instances, some features of the invention will be employed without a corresponding use of other features. Accordingly, it is appropriate that the appended claims be construed broadly and in a manner consistent with the spirit and scope of the invention herein.

05-03-00

Exhibit 21

A

LAW OFFICES
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PATENTS
TRADEMARKS
COPYRIGHTS

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May 2, 2000

EXPRESS MAIL

Assistant Commissioner for Patents
Washington, D.C. 20231

File No.: TOBINICK 3.0-010
Inventor(s): Dr. Edward L. Tobinick
Title: INTERLEUKIN ANTAGONTISTS FOR THE TREATMENT OF NEUROLOGICAL RETINAL AND MUSCULAR DISORDERS

Assignee: None

Dear Sir:

Enclosed herewith are the following documents in the above-identified application for a Letters Patent of the United States:

1 Pages of Abstract	X Verified Statement for Small Entity Status
23 Pages of Specification	Declaration, Power of Attorney & Petition
83 Number of Claims	Two (2) return-addressed postcards
none Sheets of Drawings	(PLEASE PROVIDE FILING DATE & SERIAL NUMBER)
none Assignment for Recording	(attached to copy of this letter)

Check No. 424 in the amount of $345, calculated as follows:

Basic Fee (**Large Business $690.00) (*Small Business $345.00)	$345.00
Additional Fees:	
Total number of claims 83	
Total number of claims in excess of 20, 63 times (**$18) (*$9)	567.00
Number of independent claims 8	
Number of independent claims minus 3, 5 times (**$78) (*$39)	195.00
Assignment recording fee ($40)	--
Multiple dependent claims (**$260) (*$130)	--
TOTAL filing and assignment recording fees	$1,107.00

CONVENTION DATE _____ for _____ Appln. No. _____ is claimed.
Priority Document: ____Enclosed ____Will follow

Respectfully submitted,

EZRA SUTTON, Reg No. 25,770

ES/jmt
Enclosures

INTERLEUKIN ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS

FIELD OF THE INVENTION

The present invention relates to interleukin (IL) antagonists for the treatment of neurological disorders, trauma, injuries or compression; neurodegenerative disorders including Alzheimer's Disease; demyelinating neurological disorders including multiple sclerosis; retinal disorders; and muscular disorders. More particularly, the IL antagonists are used in a new treatment of these disorders by inhibiting the action of IL in the human body. The administration of these IL antagonists is performed by intrathecal administration; intracerebroventricular administration; intranasal administration; by inhalation; or by alternative routes of administration.

BACKGROUND OF THE INVENTION

Neurological disorders due to demyelinating disease (e.g. multiple sclerosis), immune disease, inflammation, trauma, or compression, occur in different clinical forms depending upon the anatomic site and the cause and natural history of the physiological problem. Common to all of these disorders is the fact that they can cause permanent neurological damage, that damage can occur rapidly and be irreversible, and that current treatment of these conditions is unsatisfactory, often requiring surgery and/or the use of pharmacologic agents, which are often not completely successful.

DECLARATION FOR PATENT APPLICATION

Docket No. _____ 010

Exhibit 22

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled INTERLEUKIN ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS, the specification of which (check one) ☒ is attached hereto.

☐ was filed on _____ as Application Serial No. _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)
09/476,643	December 31, 1999	Pending
(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Ezra Sutton, Reg. No. 25,770

Address all telephone calls to _____ at telephone no. (732) 634-3520

Address all correspondence to EZRA SUTTON, P.A.
Plaza 9, 900 Route 9
Woodbridge, New Jersey 07095

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor Dr. Edward L. Tobinick

Inventor's signature _____ Date May 2, 2000

Residence Los Angeles, California Citizenship United States of America

Post Office Address 100 UCLA Medical Plaza
Los Angeles, California 90024-6903

Full name of second joint inventor, if any _____

Second Inventor's signature _____ Date _____

Residence _____ Citizenship _____

Post Office Address _____

(Supply similar information and signature for third and subsequent joint inventors.)

Exhibit 23

057247-0101 H8EJ

Applicant: Edward L. Tobinick

Title: INTERLEUKIN ANTAGONISTS FOR THE TREATMENT OF NEUROLOGICAL, RETINAL AND MUSCULAR DISORDERS

Patent No.: 6,471,961

Filing Date: May 2, 2000

CERTIFICATE OF EXPRESS MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service's "Express Mail Post Office To Addressee" service under 37 C.F.R. § 1.10 on the date indicated below and is addressed to: Attn: Certificate of Correction Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

EV 700371615 US (Express Mail Label Number) December 23, 2005 (Date of Deposit)

Ruthie Vallejo
(Printed Name)

(Signature)

TRANSMITTAL LETTER FOR CERTIFICATE OF CORRECTION

ATTN: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Certificate
JAN 12 2006
of Correction

Sir:

Applicant's submit herewith a certificate of correction in connection with the above-identified patent.

This certificate of correction is being filed in order to correct applicant's inadvertent omission in claiming priority to co-pending earlier filed applications under 35 U.S.C. 120.

The certificate of correction is deemed appropriate in view of the patents filing date of May 2, 2000.

Since at least one of the noted errors is not the fault of the Patent Office, the Commissioner is hereby authorized to charge the required fee of $100.00, as well as any additional fees which may be required for this Request, to Deposit Account No. 19-0741.

JAN 13 2006

Please feel free to contact the undersigned if there should be any questions.

Respectfully submitted,

Date 12-23-05

By _____

David A. Blumenthal
Attorney for Applicant
Registration No. 26,257

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5407
Facsimile: (202) 672-5399

JAN 13 2006

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,471,961 B1
DATED : October 29, 2002
INVENTOR(S) : Edward L. Tobinick

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

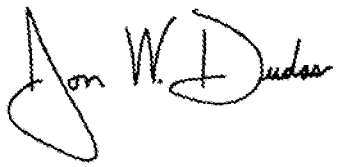
Title page,
Insert Item:

-- Related U.S. Application Data

[63] This application is a continuation-in-part of Application Serial No. 09/476,643, filed on December 31, 1999, now U.S. Patent No. 6,177,077, which is a continuation-in-part of Application Serial No. 09/275,070, filed on March 23, 1999, now U.S. Patent No. 6,015,557, which is a continuation-in-part of Application Serial No. 09/256,388, filed on February 24, 1999, now abandoned. --.

Signed and Sealed this

Twenty-third Day of May, 2006



JON W. DUDAS
Director of the United States Patent and Trademark Office

Exhibit 24.

SPE RESPONSE FOR CERTIFICATE OF CORRECTION

Paper No.: 9

DATE : 1-20-06

TO SPE OF : ART UNIT 1616

SUBJECT : Request for Certificate of Correction on Patent No.: 6,471,961

A response is requested with respect to the accompanying request for a certificate of correction.

Please complete this form and return with file, within 7 days to:
Certificates of Correction Branch ~~PK 3-922~~ South T/ 9A22
Palm location **7580** - Tel. No. 305-8309

With respect to the change(s) requested, correcting Office and/or Applicant's errors, should the patent read as shown in the certificate of correction? No new matter should be introduced, nor should the scope or meaning of the claims be changed.

Please check Related U.S. Applications

E Young

Thank You For Your Assistance

Certificates of Correction Branch

The request for issuing the above-identified correction(s) is hereby:

Note your decision on the appropriate box.

- (X) **Approved** — **All** changes apply.
- ( ) **Approved in Part** — Specify below which changes **do not** apply.
- ( ) **Denied** — State the reasons for denial below.

Comments:

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Christopher S. F. Low
SPE

1614
Art Unit

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,471,961 B1
DATED : October 29, 2002
INVENTOR(S) : Edward L. Tobinick

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Insert Item:

-- Related U.S. Application Data

[63] This application is a continuation-in-part of Application Serial No. 09/476,643, filed on December 31, 1999, now U.S. Patent No. 6,177,077, which is a continuation-in-part of Application Serial No. 09/275,070, filed on March 23, 1999, now U.S. Patent No. 6,015,557, which is a continuation-in-part of Application Serial No. 09/256,388, filed on February 24, 1999, now abandoned. --.

Signed and Sealed this

Twenty-third Day of May, 2006

JON W. DUDAS
Director of the United States Patent and Trademark Office

4-26-01

Exhibit 26

A

LAW OFFICES
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*MEMBER OF N.J. AND N.Y. BARS

April 25, 2001
BY EXPRESS MAIL

Assistant Commissioner for Patents
Washington, D.C. 20231

File No.: TOBINICK 3.0-013(CIP)
Inventor(s): Edward L. Tobinick, M.D.
Title: CYTOKINE ANTAGONISTS FOR THE TREATMENT OF LOCALIZED DISORDERS
Assignee: None

Dear Sir:

Enclosed herewith are the following documents in the above-identified application for a Letters Patent of the United States:

1 Pages of Abstract
25 Pages of Specification
38 Number of Claims
-- Sheets of Drawings
-- Assignment for Recording
X Verified Statement for Small Entity Status
Declaration, Power of Attorney & Petition
Two (2) return-addressed postcards
(PLEASE PROVIDE FILING DATE & SERIAL NUMBER)
(attached to copy of this letter)

Check No. 5397 in the amount of $1,077, calculated as follows:

Basic Fee (**Large Business $710.00) (*Small Business $355.00)	$355
Additional Fees:	
Total number of claims 38	
Total number of claims in excess of 20, 18 times (**$18)(*$9)	162
Number of independent claims 17	
Number of independent claims minus 3, 14 times (**$80)(*$40)	560
Assignment recording fee ($40)	
Multiple dependent claims (**$270) (*$135)	
TOTAL filing and assignment recording fees	**$1,077**

CONVENTION DATE None for _____ Appln. No. _____
is claimed. Priority Document: ___Enclosed ___Will follow

Respectfully submitted,

EZRA SUTTON, Reg No. 25,770

ES/jmt
Enclosures

TOBINICK 3.0-013 (CIP)

CYTOKINE ANTAGONISTS FOR THE TREATMENT OF LOCALIZED DISORDERS

RELATED APPLICATIONS

This is a continuation-in-part of Application Serial No. 09/826,976, filed on April 5, now U.S. Pat. No. 6,419,949, 2001, which is a continuation-in-part of Application Serial No. 09/563,651, filed on May 2, now U.S. Pat. No. 6,471,961, 2000, which is a continuation-in-part of Application Serial No. 09/476,643, filed on December 31, 1999, now U.S. Patent No. 6,177,077, which is a continuation-in-part of Application Serial No. 09/275,070, filed on March 23, 1999, now U.S. Patent No. 6,015,557, which is a continuation-in-part of Application Serial No. 09/256,388, filed on February 24, 1999, now abandoned.

FIELD OF THE INVENTION

The present invention relates to specific cytokine antagonists which are provided for the treatment and prevention of damage to the optic nerve, other cranial nerves, brain, spinal cord, nerve roots, peripheral nerves or muscles caused by any one of the following: a herniated nucleus pulposus, osteoarthritis, other forms of arthritis, disorders of bone, disease, or trauma. More particularly, the cytokine antagonists are used in a new treatment of these disorders utilizing localized anatomic administration which causes inhibition of the action of the corresponding pro-inflammatory cytokine in a localized anatomic area of the human body. The administration of these cytokine antagonists is performed by anatomically localized administration which includes, but is not limited to the following routes:

DECLARATION FOR PATENT APPLICATION

Docket No. TOBINICK 3.0-013 (CIP)

Exhibit 27

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled CYTOKINE ANTAGONISTS FOR THE TREATMENT OF LOCALIZED DISORDERS, the specification of which

(check one) ☒ is attached hereto.
☐ was filed on _____ as
Application Serial No. _____
and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application: 09/826,976, filed April 5, 2001, pending

(Application Serial No.)	(Filing Date)	(Status—patented, pending, abandoned)
09/563,651	May 2, 2000	Pending
09/476,643	December 31, 1999	Patented
09/275,070	March 23, 1999	Patented
09/256,388	February 24, 1999	Abandoned

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Ezra Sutton, Reg. No. 25,770

Address all telephone calls to _____ at telephone no. (732) 634-3520

Address all correspondence to EZRA SUTTON, P.A.
Plaza 9, 900 Route 9
Woodbridge, New Jersey 07095

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor DR. EDWARD L. TOBINICK
Inventor's signature _____ Date April 20, 2001
Residence Los Angeles, California 90024-6903 Citizenship United States of America
Post Office Address 100 UCLA Medical Plaza, Suite 205
Los Angeles, California 90024-6903

Full name of second joint inventor, if any _____
Second Inventor's signature _____ Date _____
Residence _____ Citizenship _____
Post Office Address _____

(Supply similar information and signature for third and subsequent joint inventors.)

CYTOKINE ANTAGONISTS FOR THE TREATMENT OF LOCALIZED DISORDERS

RELATED APPLICATIONS

This is a continuation-in-part of application Ser. No. 09/826,976, filed on Apr. 5, 2001, now U.S. Pat. No. 6,419,944 which is a continuation-in-part of application Ser. No. 09/563,651, filed on May 2, 2000, was U.S. Pat. No. 6,471,961, which is a continuation-in-part of application Ser. No. 09/476,643, filed on Dec. 31, 1999, now U.S. Pat. No. 6,177,077, which is a continuation-in-part of application Ser. No. 09/275,070, filed on Mar. 23, 1999, now U.S. Pat. No. 6,015,557, which is a continuation-in-part of application Ser. No. 09/256,388, filed on Feb. 24, 1999, now abandoned.

FIELD OF THE INVENTION

The present invention relates to specific cytokine antagonists which are provided for the treatment and prevention of damage to the optic nerve, other cranial nerves, brain, spinal cord, nerve roots, peripheral nerves or muscles caused by any one of the following: a herniated nucleus pulposus, osteoarthritis, other forms of arthritis, disorders of bone, disease, or trauma. More particularly, the cytokine antagonists are used in a new treatment of these disorders utilizing localized anatomic administration which causes inhibition of the action of the corresponding pro-inflammatory cytokine in a localized anatomic area of the human body. The administration of these cytokine antagonists is performed by anatomically localized administration which includes, but is not limited to the following routes: perilesional; intralesional; and transepithelial (for disorders of the optic nerve). Perilesional routes as mentioned above include, but are not limited to, subcutaneous, intramuscular, and epidural routes of administration.

BACKGROUND OF THE INVENTION

Localized administration for the treatment of localized clinical disorders has many clinical advantages over the use of conventional systemic treatment. Locally administered medication after delivery diffuses through local capillary, venous, arterial, and lymphatic action to reach the anatomic site of neurologic or muscular dysfunction; or in the case of the eye through the conjunctiva, then through the aqueous and vitreous humor to reach the optic nerve and retina.

All of the cytokine antagonists which are currently available have been developed for systemic administration. This is because all were developed to treat systemic illnesses, including rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, and Crohn's Disease. Systemic illnesses by definition require systemic treatment.

The use of cytokine antagonists to treat localized disorders is discussed in U.S. Pat. Nos. 6,015,557 and 6,177,077 and other pending applications of the applicant. This invention includes further applications of these ideas.

Localized administration, including perilesional or intralesional administration, when compared to systemic administration, carries with it one or more of the following advantages:

1) greater efficacy due to the achievement of higher local concentration;

2) greater efficacy due to the ability of the administered therapeutic molecule to reach the target tissue without degradation caused by hepatic or systemic circulation;

3) more rapid onset of action;

4) longer duration of action; and

5) Potentially fewer side effects, due to lower required dosage.

Pilot studies conducted by the inventor for one of the disorders discussed herein, herniated nucleus pulposus, have demonstrated the dramatic efficacy, and the extraordinarily rapid onset of action of perilesional administration in this clinical disorder. Ongoing pilot studies for other clinical conditions also demonstrate positive results.

Neurological disorders due to a herniated nucleus pulposus, osteoarthritis, other forms of arthritis, disorders of bone, disease, or trauma causing damage to the optic nerve, other cranial nerves, spinal cord, nerve roots, or peripheral nerves are common and cause considerable morbidity in the general population. Common to all of these disorders is the fact that they can cause permanent neurological damage, that damage can occur rapidly and be irreversible, and that current treatment of these conditions by pharmacologic or other means is often unsatisfactory. Surgical treatment is therefore often required, and is not uniformly successful.

Of these neurological disorders, radiculopathy due to a herniated nucleus pulposus is among the most common. This condition occurs in both the lumbar and cervical regions. Lumbar radiculopathy due to the herniation of a lumbar intervertebral disc causes sciatica i.e. pain in the lower back with radiation to a leg. Neurologic symptoms and signs are often present, including numbness, paresthesia, and motor symptoms involving the leg or foot. Cervical radiculopathy caused by a herniated nucleus pulposus in the cervical region causes pain and neurologic symptoms in the neck and an upper extremity. Other localized neurological conditions include acute spinal cord trauma, spinal cord compression, spinal cord hematoma, cord contusion (these cases are usually traumatic, such as motorcycle accidents or sports injuries); acute or chronic spinal cord compression from cancer (this is usually due to metastases to the spine, such as from prostate, breast or lung cancer); and carpal tunnel syndrome. Localized disorders of the cranial nerves include Bell's Palsy; and glaucoma, caused by glaucomatous degeneration of the optic nerve.

Pharmacologic agents used in the past to treat these disorders have included corticosteroids. Corticosteroid administration, however, may cause multiple side effects, and is often ineffective.

Newer biopharmaceutical medications have been developed which have been shown to offer dramatic clinical benefit for systemic illnesses in humans, even for those disorders which have not responded to large and repeated doses of corticosteroids. These biopharmaceutical medications fall into the category of cytokine antagonists because they block, or antagonize, the biologic action of a specific cytokine which has adverse clinical effects. These cytokines include members of the interleukin class and tumor necrosis factor.

Tumor necrosis factor (TNF) is intimately involved in the nervous system and in inflammatory disorders of muscle. It is central to the response to injury, either virally induced, disease induced, or occurring as a result of mechanical trauma. TNF is also central to neuronal apoptosis, a process important in many neurological disorders.

Specific inhibitors of TNF, only recently commercially available, now provide the possibility of therapeutic intervention in TNF mediated disorders. These agents have been developed to treat systemic illnesses, and therefore have been developed for systemic administration. Various biopharmaceutical companies have developed TNF antagonists to treat systemic illnesses: Immunex Corporation developed etanercept (Enbrel®) to treat rheumatoid arthritis; Johnson